FDA Executive Summary

Prepared for the
May 22, 2013 Meeting of the
Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee

Classification Discussion
Pedicle Screw Spinal Systems (Certain Uses - Class III Indications for Use)

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1. Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), the Food and Drug Administration (FDA) is convening the Orthopaedic and Rehabilitation Devices Advisory Panel (the panel) for the purpose of obtaining recommendations regarding certain Class III uses of pedicle screw spinal systems in the thoracolumbosacral spine that were subject to orders under Section 515(i). This section of the Act requires FDA to order manufacturers of preamendments Class III devices for which no final regulation has been issued requiring the submission of premarket applications (PMAs) to submit to the FDA a summary of, and a citation to, any information known or otherwise available to them respecting such devices, including adverse safety and effectiveness information that has not been submitted under other sections of the Act.

Industry responded to FDA's April 9, 2009 Federal Register (FR) Notice [Docket No. FDA-2009-M-0101] requiring safety and effectiveness information under Section 515(i) (i.e., 515(i) Order) for usage of pedicle screw spinal systems in the thoracolumbosacral spine for treatment of degenerative disc disease (DDD) and types of spondylolisthesis other than severe spondylolisthesis (grades 3 or 4) or degenerative spondylolisthesis with objective evidence of neurologic impairment referred to hereafter as Class III spondylolisthesis. The 515(i) Order was issued to determine whether the classification for the devices with these specific indications for use should remain as Class III and require a premarket approval (PMA) application or be downclassified into Class I (General Controls) or Class II (General and Special Controls).

The panel will be asked to provide input on the FDA's proposed classification strategy for pedicle screw spinal systems for use in the thoracolumbosacral spine for treatment of DDD and types of spondylolisthesis other than severe spondylolisthesis (grades 3 or 4) or degenerative spondylolisthesis with objective evidence of neurologic impairment, into Class II (Special Controls). Please note that for a subtype of pedicle screw spinal systems, namely dynamic stabilization systems (see Section 6.3), FDA does not believe Special Controls can necessarily be developed to mitigate the risks to health. Consequently, FDA is currently recommending that dynamic stabilization systems should be found to remain as Class III. The panel will also be requested to specifically discuss the risks to health associated with dynamic stabilization systems, whether the identified risks can be mitigated with appropriate special controls, and whether this device type fits the statutory definition for a Class III device.

2. Device Description

<u>As currently defined in 21 CFR 888.3070:</u>

(a) *Identification.* Pedicle screw spinal systems are multiple component devices, made from a variety of materials, including alloys such as 316L stainless steel, 316LVM stainless steel, 22Cr-13Ni-5Mn stainless steel, Ti-6Al-4V, and unalloyed titanium, that allow the surgeon to build an implant system to fit the patient's anatomical and physiological requirements. Such a spinal implant assembly consists of a combination of anchors (e.g., bolts, hooks, and/or screws); interconnection

mechanisms incorporating nuts, screws, sleeves, or bolts; longitudinal members (e.g., plates, rods, and/or plate/rod combinations); and/or transverse connectors.

Modern pedicle screw spinal systems are comprised of longitudinal members(rods), spinal anchors (screws, hooks and/or wires) and optional transverse connectors. These components are used to stabilize single or multiple spinal motion segments from the upper thoracic spine to the sacrum as an adjunct to spinal fusion. Presently, pedicle screws are the most commonly utilized spinal anchor and linkage to longitudinal members (e.g., rods, plates, rods, and/or hybrid plate/rod configurations) is achieved through an interconnection mechanism (e.g., offset connector, nuts, screws, sleeves, or bolts).

3. Current Classification

As currently defined in 21 CFR 888.3070:

(b) *Classification.* (1) Class II (special controls), when intended to provide immobilization and stabilization of spinal segments in skeletally mature patients as an adjunct to fusion in the treatment of the following acute and chronic instabilities or deformities of the thoracic, lumbar, and sacral spine: severe spondylolisthesis (grades 3 and 4) of the L5-S1 vertebra; degenerative spondylolisthesis with objective evidence of neurologic impairment; fracture; dislocation; scoliosis; kyphosis; spinal tumor; and failed previous fusion (pseudarthrosis).
(2) Class III (premarket approval), when intended to provide immobilization and stabilization of spinal segments in the thoracic, lumbar, and sacral spine as an adjunct to fusion in the treatment of degenerative disc disease and spondylolisthesis other than either severe spondylolisthesis (grades 3 and 4) at L5-S1 or degenerative spondylolisthesis with objective evidence of neurologic impairment.

It should be noted that this classification regulation is currently split between Class II and Class III. Although the focus of this panel today is primarily on 888.3070(b)(2) of the classification regulation, it should be noted that some elements of the discussion may also be relevant to modifications that could eventually impact part (b)(1). Any modifications to 888.3070(b)(1) are subject to a different regulatory process.

4. Classification and Regulatory History

A brief summary of the regulatory history for pedicle screw spinal systems, particularly when used in the thoracolumbosacral spine, is provided within this section.

1993 Classification Panel Meeting

In 1993, the FDA requested data related to all pedicle screw fixation systems, which were unclassified at the time. The 1993 classification panel meeting was the first in which postamendments (devices not on the market prior to May 28, 1976) pedicle screw fixation systems were discussed. Specifically, the panel discussed the concept of a historical cohort study, which would provide clinical information on the use of pedicle screw fixation in thoracic, lumbar, and lumbosacral fusions.

1994 Classification Panel Meeting
This second classification panel meeting was held to present a compilation of data regarding the use of pedicle screw fixation, primarily as an adjunct to fusion in the thoracolumbosacral spine. Based on this information, the panel agreed that pedicle screw spinal systems were most appropriate for treatment of spinal instabilities (i.e., trauma, deformity, tumor reconstruction, spondylolisthesis). In general, the panel did not support classifying pedicle screw spinal systems as an adjunct to fusion in treating a patient population with degenerative disc disease (DDD) as Class II (special controls) at that time because of the lack of sufficient safety and effectiveness data, as well as the lack of clarity surrounding the definition of this disorder. In addition, the reported treatment outcomes for DDD population were considered to potentially be device-dependent based on data available at that time. At this meeting, the panel identified device-related and operative risks to health (please see Section 8).

The 1993 and 1994 Classification panel meetings did not discuss use of screws in the cervical spine and remained silent on screw use in skeletally immature patients (i.e., a subset of pediatric patients, as defined by the FDA).

1995 Classification Proposed Rule
On October 4, 1995 (60 FR 51946), the FDA issued a proposed rule regarding the classification of pedicle screw spinal systems, specifically on the recommendations of the panel regarding this proposed classification. The panel recommended that the FDA classify into Class II the previously unclassified preamendments pedicle screw spine systems intended for the treatment of severe spondylolisthesis (grades 3 and 4) at the L5-S1 level. The panel also recommended that the postamendments pedicle screw spinal systems intended for degenerative spondylolisthesis and spinal trauma be reclassified from Class III to Class II. For all other indications, these pedicle screw spinal systems were considered to be postamendments Class III devices, for which a PMA application was required. The FDA further proposed to expand the intended uses of the device to include pedicle screw spinal systems intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion in the treatment of acute and chronic instabilities and deformities, including spondylolisthesis, fractures and dislocations, scoliosis, kyphosis, and spinal tumors.

1998 Classification Final Rule
On July 27, 1998 (63 FR 40025), after receiving and addressing comments to the 1995 proposed rule for classification of pedicle screw spinal systems as an adjunct to fusion, thoracolumbosacral pedicle screw spinal systems were classified as Class II devices for the following indications: degenerative spondylolisthesis with objective evidence of neurologic impairment, fracture, dislocation, scoliosis, kyphosis, tumor, and failed previous fusion. DDD was specifically excluded due to a lack of conclusive clinical data and is still considered Class III. In addition, this final rule was silent regarding use of pedicle screws in the cervical spine and in skeletally immature patients.

2001 Publication of Technical Amendment
A technical amendment was published on May 22 2001 (66 FR 28051) to correct the omission of one intended use – the use of pedicle screw spinal systems in the treatment of severe spondylolisthesis (grades 3 and 4) at the L5-S1 level as an adjunct to fusion. This indication was found to fall under preamendments status as devices were marketed for this indication prior to 1976.

The technical amendment also clarified that the use of pedicle screw spinal systems in a skeletally immature population, as well as cervical use, remained unclassified. However, it is now understood that pediatric uses of pedicle screw spinal systems that cover a skeletally immature population were cleared through the 510(k) regulatory process prior to the issuance of this technical amendment, resulting in a classification decision that designated such systems for these uses as Class II.[1]

2009 515(i) Order
Through the April 9, 2009 515(i) Order (74 FR 16214), the FDA requested safety and effectiveness information on the remaining preamendment Class III 510(k) device types, to determine appropriate classification. Included in the list of premendment Class III 510(k) device types were pedicle screw spinal systems for use in the thoracolumbosacral spine as an adjunct to fusion for treatment of degenerative disc disease and Class III spondylolisthesis (21 CFR 888.3070(b)(2)).

5. Responses to April 9, 2009 515(i) Order

FDA received responses to the 515(i) Order, either individually, or collectively as part of the response submitted by the Orthopedic Surgical Manufactures Association (OSMA), from the following companies: Aesculap Implant Systems, Alphatec Spine, Blackstone Medical (now Orthofix), DePuy Spine, EBI (d/b/a Biomet Spine), Globus Medical, Innovasis, LANX, LDR Spine USA, Lifespine, Medtronic Spinal and Biologics, Paradigm Spine, Pioneer Surgical, Seaspine, Spinal Elements, Stryker Spine, Synthes Spine, Ulrich Medical, VertiFlex, and Zimmer Spine. Comments to the 515(i) Order on the public docket unanimously recommended reclassification of pedicle screw spinal systems as an adjunct to fusion for DDD and Class III spondylolisthesis into Class II.

Certain respondents did not limit their reclassification recommendations to the pedicle screw uses described in 21 CFR 888.3070(b)(2). For example, the recommendations prepared by OSMA in response to the 515(i) Order recommended classification of pedicle screw spinal systems when used to treat pediatric deformities in skeletally immature patients into Class II. Medtronic Spinal and Biologics also recommended the classification of pediatric deformity uses from unclassified to Class II. However, as stated above in Section 4, the pediatric indications (which incorporate skeletally immature patients) have already been classified as Class II.

[1] K980761, "When labeled for pedicle screw fixation… is intended for use in grade 3 or 4 spondylolisthesis at the fifth lumbar-first sacral vertebra joint (L5-S1)… for pediatric patients with a body weight of 50 lbs or less.", See Appendix A.

Additionally, Globus Medical proposed revising the regulatory definition of DDD to remove "discogenic origin" and state "degeneration of the disc confirmed by history of back pain and demonstrated by radiographic studies".

The Panel will be asked to comment on whether "skeletally mature" or "skeletally immature" terminology is an adequate qualification or whether such a qualification is necessary in the indications for use within the classification regulation 21 CFR 888.3070.

6. Background: Pedicle Screw Spinal System Types and Uses

Pedicle screw fixation in the thoracic and lumbar spine was first performed in Europe for treatment of spinal fractures by Roy-Camille (Roy-Camille, 1976) and subsequently extended to treatment of spinal instabilities secondary to a range of spinal pathologies including spinal tumors, non-unions following prior spinal fusions, spondylolisthesis, spinal deformities (i.e., scoliosis, kyphosis) and various lumbar degenerative disorders (Louis,1986; Magerl, 1984). In the United States, Harrington advanced the concept of posterior internal fixation of the spine, and first described use of pedicle screws in combination with fusion for treatment of severe spondylolisthesis in adolescent patients (Harrington, 1969). Harrington instrumentation provided a method for initial correction of spinal deformity, and achieved long term stabilization through spinal fusion. Harrington's method represented an important advancement as it improved the rate of successful arthrodesis and minimized the progressive loss of deformity correction that accompanied posterior spinal fusion performed without use of internal fixation. However, as the original Harrington system achieved fixation limited to the proximal and distal end vertebra via hooks, alternative systems were developed to address deficiencies of the Harrington system, which included hook dislodgement, a requirement for rigid postoperative bracing, inability to perform short segment fixation following laminectomy, and limited control of sagittal alignment of the spine leading to the loss of normal lumbar lordosis when distraction forces were utilized in the lumbar region (Harrington, 1988).

Posterior spinal systems intended for fusion indications were subsequently developed, which achieved segmental fixation to the posterior spinal elements at multiple fixation points (lamina, spinous process, pedicle) using wires or cables (Luque, 1982; Songer, 1991), hooks (Cotrel, 1988), and/or screws (Steffee, 1986; Asher, 2004). Pedicle fixation evolved as the preferred method for achieving posterior segmental fixation in the thoracic and lumbar spine as the location of the pedicle at the junction between the posterior spinal elements and the vertebral body provides the most secure fixation site, and permits stabilization of the spine even in the absence of intact posterior spinal elements (Gaines, 2000). A wide range of pedicle screw spinal systems for use as an adjunct to fusion have evolved and share common features including pedicle screw bone anchors, rigid longitudinal members (i.e., plates, rods, and/or plate/rod combinations), interconnection mechanisms to achieve screw-rod linkage, and transverse connectors to link longitudinal members.

Fusion is defined in a variety of ways in the clinical literature, as uniform criteria for assessment of fusion success remain controversial. Criteria used to define fusion include assessment of bridging bone and/or segmental spinal motion on imaging studies. These criteria may be assessed in the interbody space or the posterior spinal elements, depending on the fusion method and location of bone graft. The fusion definitions used in the literature, which is presented and analyzed in this Executive Summary, vary by investigator. The fusion rates reported are relative to the investigator or institution's definition of success.

A variety of fusion techniques are utilized in conjunction with pedicle screw spinal systems for treatment of patients with DDD and spondylolisthesis. These fusion techniques include posterior fusion (posterolateral or intertransverse fusion, facet fusion) and fusion of the anterior spinal column (interbody fusion). Interbody fusion techniques include ALIF (anterior lumbar interbody fusion), PLIF (posterior lumbar interbody fusion), and TLIF (transforaminal lumbar interbody fusion).

6.1 Background: Spondylolisthesis

6.1.1 Clinical Significance of Spondylolisthesis Grades and Types

Spondylolisthesis is defined as anterior displacement of a vertebra in relation to the subjacent vertebra. Severity of spondylolisthesis is most commonly quantified according to the amount of translation of the superior vertebra in relation to the subjacent vertebra and termed as grade 1 (1-25% translation), grade 2 (26-50% translation), grade 3 (51%-75% translation), grade 4 (76-100% translation), and grade 5 (slippage of the L5 vertebra anterior and distal to the superior aspect of the S1 endplate, termed "spondyloptosis"). A universally accepted classification for different types of spondylolisthesis does not exist. Based on anatomic features, Wiltse (Wiltse, 1976) initially distinguished 5 types of spondylolisthesis, and the classification was subsequently expanded to include postsurgical spondylolisthesis as a sixth type (Table 1).

Table 1: Classification of Spondylolisthesis-Wiltse *et al.*

Type 1	Dysplastic: Associated with congenital anomalies involving the L5-S1 articulation
Type 2	Isthmic: Associated with a lesion involving the pars interarticularis
	Subtype 2A: Lytic defect (stress fracture in the pars interarticularis)
	Subtype 2B: Elongated or attenuated pars
	Subtype 2C: Acute pars fracture
Type 3	Degenerative
Type 4	Traumatic
Type 5	Pathologic
Type 6	Postsurgical or Iatrogenic

An alternative classification (Marchetti and Bartolozzi, 1982,1997) stratified spondylolisthesis into two major subgroups – developmental and acquired – based on the presence or absence of dysplasia (abnormal tissue development) at the level of slippage (see Table 2). Dysplastic features that may be present include lumbosacral facet anomalies,

deficient L5-S1 lamina, elongation of the pars interarticularis, rounding of the upper sacrum, and a trapezoidal-shaped L5-S1 vertebral body and may be present to varying degrees in each patient.

Table 2: Marchetti and Bartolozzi Classification of Spondylolisthesis

Developmental	Acquired
High dysplasia -With lysis -With elongation Low dysplasia -With lysis -With elongation	Degenerative Post surgical Traumatic Pathologic

More recent classifications incorporate additional factors including sacropelvic morphology and spinopelvic balance to guide surgical treatment (Mac-Thiong, 2012). Classification systems for spondylolisthesis generally do not distinguish between pediatric and adult patients.

Degenerative Spondylolisthesis
The most common type of spondylolisthesis is the degenerative type, which occurs only in adult patients as a consequence of degenerative changes occurring in the intervertebral disc space and/or facet joints. Notably, in the absence of prior surgery, degenerative spondylolisthesis presents with slippage less than 50% (i.e., grades 1 or 2) as the intact posterior spinal elements limit further progression.

Isthmic Spondylolisthesis
The next most common type of spondylolisthesis is broadly classified as the "isthmic type," according to the Wiltse classification, and may be conceptualized as an acquired lytic defect in the pars interarticularis region of the posterior arch, which occurs most commonly between ages 5-20 years. This form of spondylolisthesis occurs most commonly at L5-S1 level and is most commonly associated with low grade slippage (grades 1 and 2). It should be recognized that overlap between the isthmic and dysplastic types of spondylolisthesis exists in the literature as studies often do not always differentiate between acquired stress fractures through normal posterior elements and fractures occurring through dysplastic posterior spinal elements (Hammerberg, 2005).

Dysplastic Spondylolisthesis
The dysplastic type of spondylolisthesis includes a broad spectrum of patients ranging from low dysplastic forms, which lead to symptoms in early adulthood, to high dysplastic forms, which lead to severe symptoms and high grade slippages (grades 3, 4 and 5) in adolescence. It should be noted that dysplastic spondylolisthesis is not generally present at birth and develops in association with growth, skeletal remodeling, and as a consequence of upright posture (Hammerberg, 2005).

Post-Surgical, Pathologic and Traumatic Spondylolisthesis

Additional sub-categories of spondylolisthesis include: post-surgical, pathologic, and traumatic types. Post-surgical spondylolisthesis most commonly occurs as a consequence of removal of bone and/or soft tissue structures during posterior decompression of neural structures. The likelihood of occurrence of post-surgical spondylolisthesis is increased in the presence of preoperative risk factors that predispose to subsequent instability as well as following intraoperative structural alterations that compromise spinal stability (e.g., excessive facet joint removal, pars fracture). Pathologic subtypes of spondylolisthesis arise as a consequence of the inability of the posterior spinal elements to resist forward displacement of the involved vertebra on the subjacent vertebra due to local or general bone disease (e.g., osteogenesis imperfecta). Traumatic spondylolisthesis results from an acute fracture in a region of the posterior spinal elements other than the pars interarticularis.

6.1.2 Regulatory Status of Spondylolisthesis

Pedicle screw spinal systems as an adjunct to fusion are Class II (Special Controls) when intended to provide immobilization and stabilization of spinal segments in skeletally mature patients with severe spondylolisthesis (grades 3 and 4) at the L5-S1 level, or for use in treatment of degenerative spondylolisthesis with objective evidence of neurologic impairment. Thus, the existing regulatory classification effectively considers use of pedicle screw spinal systems as Class II for treatment of specific subtypes of spondylolisthesis ranging from grade 1 through grade 4, because degenerative spondylolisthesis, by its pathophysiology, is limited to grades 1 and 2, while higher grades of "severe" spondylolisthesis (grades 3 and 4) are considered Class II indications (Table 3). However, the same pedicle screw spinal systems are currently considered Class III when used for "other" subtypes of spondylolisthesis. This group of "other" spondylolisthesis consists of grade 1 and grade 2 non-degenerative spondylolisthesis. The major group of spondylolisthesis not included within the current Class II indications for pedicle screw spinal systems is low-grade (grades 1 and 2) isthmic spondylolisthesis.

Table 3: Spondylolisthesis Types in Relation to Current FDA Regulatory Status

Type	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Degenerative Type	Class II**	Class II**	n/a*	n/a*
Other Types	Class III - To be considered by panel	Class III - To be considered by panel	Class II***	Class II***

* Degenerative spondylolisthesis, by its pathophysiology, is limited to grades 1 and 2.
** Degenerative spondylolisthesis with objective evidence of neurologic impairment.
*** Grades 3 and 4 severe spondylolisthesis at L5-S1

Note that for the purpose of this review, specific types of spondylolisthesis are not considered for additional analysis. Traumatic spondylolisthesis is considered as included within the existing Class II indications related to pedicle screw spinal systems as this condition may be considered as a specific type of fracture and/or dislocation. Patients with degenerative spondylolisthesis without objective evidence of neurologic impairment are not considered as constituting a clinically relevant population subset that merits additional

analysis because according to current standard medical practice, spinal fusion with pedicle fixation is not generally indicated in the absence of symptoms related to radiculopathy or spinal stenosis in the absence of a history of prior spine surgery at the same spinal segment.

In addition, it is necessary to recognize that patients with degenerative spondylolisthesis within grade 1 have been considered previously by FDA as a subset contained within the population termed as having DDD (See PMAs P050010[2], P040006[3]). Within these studies, this population (DDD with up to grade 1 spondylolisthesis) was treated with standard of care surgical treatment for a DDD population, and considered a control group for comparison with an investigational treatment.

6.2 Background: Degenerative Disc Disease

6.2.1 Clinical Significance of Degenerative Disc Disease

Degeneration of the intervertebral disc, commonly termed DDD, is a complex process that may start in early life as a result of genetic, physiologic, and environmental factors, as well as normal aging. The high prevalence of the degenerative process in both symptomatic and asymptomatic subjects limits the ability to correlate anatomic derangement and clinical symptoms (Modic, 2007). Because a standardized clinical definition of DDD does not exist, systems of measurement vary between studies and limit meaningful study comparisons. It has been noted that current measures of disc degeneration lack adequate reliability and precision (Battie, 2006).

Current thoracolumbosacral pedicle screw spinal systems are regulated as Class III devices, when intended to provide immobilization and stabilization of spinal segments in the thoracic, lumbar, and sacral spine as an adjunct to fusion for treatment of DDD. The focus of this panel meeting is to discuss whether or not to reclassify the Class III indications for pedicle screw spinal systems, including DDD. The purpose of this meeting is not to discuss comparative effectiveness of alternative treatments, including but not exclusively limited to non-operative treatment, non-instrumented posterior fusion, anterior interbody fusion, or total disc arthroplasty. FDA recognizes and emphasizes that the primary treatment for the majority of patients with low back pain associated with the condition referred to as DDD is nonoperative and that patients treated with surgical intervention are selected from the population of patients who have failed extensive non-operative management. FDA is also aware that assessment of the relationship between clinical symptoms, imaging findings, and treatment outcomes for patients with DDD requires precise and accurate stratification of patient cohorts. In addition, it is recognized that the interaction of socioeconomic, psychosocial, and genetic factors in the presence of degenerative spinal pathology is an important consideration and that there exists considerable uncertainty regarding the relative contribution of such factors based on the present body of scientific knowledge. Many of these factors fall outside of FDA's authority in regulating device manufacturers and within the scope of practice of medicine.

[2] SSED P050010, http://www.accessdata.fda.gov/cdrh_docs/pdf5/P050010b.pdf
[3] SSED P040006, http://www.accessdata.fda.gov/cdrh_docs/pdf4/P040006b.pdf

6.2.2 Regulatory Status of Degenerative Disc Disease

Regulatory definitions for DDD are variable (Table 4) and rely on combinations of clinical symptoms (back and/or radicular pain), physical examination findings, and imaging modalities (radiographs, CT, MRI, discography, myelography) that consider degeneration of various components of the spinal motion segment, including the disc, vertebral endplates, ligamentum flavum, facet joint capsules, and facet joints. In addition, regulatory definitions of DDD have included subjects with grade 1 degenerative spondylolisthesis (PMA P050010) and subjects with a history of prior spinal procedures including discectomy, laminotomy, laminectomy, or nucleolysis at the target spinal level (PMA P040006).

Table 4: Published/Recognized Definitions for Degenerative Disc Disease (DDD)

FDA Source Document	Definition
*Guidance Document for the Preparation of IDEs for Spinal Systems (2000)**	"DDD should be based on patient history and radiographic studies. FDA suggests that the sponsor consider the following: DDD should be defined as back and/or radicular pain with degeneration of the disc as confirmed by patient history, physical examination, and radiographic studies with 1 or more of the following factors (as measured radiographically, either by CT, MRI, plain film, myelography, discography, etc.): • instability as defined by 3mm translation or 5° angulation; • osteophyte formation of facet joints or vertebral endplates; • decreased disc height, on average by >2mm, but dependent upon the spinal level; • scarring/thickening of ligamentum flavum, annulus fibrosis, or facet joint capsule; • herniated nucleus pulposus; • facet joint degeneration/changes; and/or • vacuum phenomenon"
*Guidance for Industry and FDA Staff: Spinal System 510(k)s***	"DDD is defined as neck or back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies"
FDA Summary of Safety and Effectiveness Data (P050010), Indications for Use	"DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. These DDD patients should have no more than grade 1 spondylolisthesis at the involved level."
FDA Summary of Safety and Effectiveness Data (P040006), Inclusion Criteria	Diagnosis of DDD includes "subjects with a history of prior spinal procedures including discectomy, laminotomy, laminectomy, or nucleolysis at the target spinal level"

*http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073772.pdf

**http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm072459.htm

Anatomically, at each level of the spine, the articulation between adjacent vertebra consists of the intervertebral disc and two posterior facet joints (zygoapophyseal joints). The spinal motion segment consists of two adjacent vertebrae, the intervening intervertebral disc and related spinal ligments, and represents the functional unit of the spinal column. Lesions which affect the intervertebral disc may also affect the facet joints and vice versa (Kirkaldy-Willis, 1978). Subsequently, the posterior ligaments of the lumbar spine, as well as the facet joints and disc, may interact with each other leading to advanced degeneration of all components of the spinal motion segment (Iida, 2002), and may or may not lead to impingement upon adjacent neural structures. Spinal deformities may subequently develop as the structural integrity of the spinal motion segment is compromised by the degenerative process. Unisegmental spinal deformities (i.e., degenerative spondylolisthesis) or multisegmental spinal deformities (i.e., scoliosis, kyphosis) may develop, and may or may not be associated with pain and/or neurologic symptoms secondary to disc displacement or spinal stenosis.

As the degenerative process encompassed by the term "degenerative disc disease" reflects a biologic and mechanical process that interactively influences the integrity of all components of the spinal motion segment (i.e., disc, facet joints, ligaments) and related neural elements, it has been suggested that the term "degenerative spine pathology (DSP)" replace the term "degenerative disc disease (DDD)" in order to more accurately reflect the spectrum of anatomic structures involved in the degenerative process. It is important to appreciate that despite completion of systematic reviews to determine the natural history of degeneration of the lumbar and cervical spine (Lee, 2012), lack of consensus regarding the definition and classification of spinal degeneration persists. It has been recommended that use of simple descriptive terminology for spinal degeneration is preferable and that distinction between degenerative spinal pathology which is noted solely on the basis of imaging studies, and degenerative spinal pathology which is associated with clinical signs and symptoms is critical (Riew, 2012).

The panel will be asked to comment on the use of the term, "Degenerative Disc Disease", or DDD, potential use of an alternative, more encompassing definition of "Degenerative Spinal Pathology" or "DSP." The panel will also be asked to comment on any additional factors to consider regarding distinction between symptomatic and asymptomatic spinal degeneration, as well as the need to identify clinically relevant subgroups in the DDD/DSP population .

7. Summary of Clinical Evidence

7.1 Targeted Literature Review: Class III Indications of Pedicle Screw Spinal Systems

7.1.1 Methods

A survey of current literature related to thoracolumbosacral fusion with pedicle fixation systems for treatment of spondylolisthesis and DDD was performed to assess current surgical practice and reported treatment outcomes over the past two decades.

Due to recognized limitations associated with the current medical literature related to spinal fusion for treatment of spondylolisthesis and DDD (i.e., heterogeneity, disparate study methodologies, lack of precise diagnostic criteria), a critical review of relevant literature was considered the most appropriate method to ascertain the current status regarding use of pedicle screw spinal systems rather than analysis based on methodologic design criteria. PubMed, a service of the National Library of Medicine, was searched in two phases: 1) for articles published in the past 15 years (June 1, 1994 to April 30, 2009), and 2) for articles published over the past 4 years (May 1, 2009 to March 8, 2013). The rationale for the bipartite search structure was based on the existence of a comprehensive literature search previously submitted to FDA by OSMA in their response to the April 9, 2009 515(i) Order. The present search strategy was intended to both confirm the initial search results (1994-2009) submitted by OSMA, and to extend the search using identical search parameters (see Docket No. FDA-2009-M-0101) to investigate more recent literature through the present day. OSMA identified a total of 21 articles for inclusion in their analysis, published between June 1, 1994 and April 30, 2009. To extend the search through the present day, a total of 324 additional titles/abstracts published between May 1, 2009 and March 8, 2013, were listed and reviewed (i.e., 237 degenerative disc disease (DDD) and 87 spondylolisthesis), and of these, 10 articles were retrieved and reviewed.

A summary of the effectiveness results derived from the above analyses are presented in Tables 5 and 6. Safety results were abstracted and tabulated in Table 7. In addition, the results from the studies considered in this review are compared to the results of the historical cohort study (Yuan 1994), which included an analysis of degenerative spondylolisthesis subjects, and was utilized in support of classification of pedicle screws to Class II for various indications (1993 and 1994 Panel meetings, discussed above). See Section 11 for references.

7.1.2 Safety and Effectiveness: Class III Spondylolisthesis

The rationale for use of pedicle fixation in the treatment of Class III spondylolisthesis indications such as low-grade isthmic spondylolisthesis relates to the ability of rigid spinal instrumentation to treat associated spinal instability by limiting strain during the process of fusion healing thereby enhancing fusion success (Mardjetko, 2011). The focus of this literature review, therefore, concerns assessment of effectiveness in terms of fusion (Table 5) and safety in terms of adverse events (Table 7) of pedicle screw spinal systems for treatment of spondylolisthesis (Class III indications), as compared to known effectiveness and safety data that exist for other cleared uses of pedicle screw spinal systems as an adjunct to spinal fusion (Class II indications). The control group for this review consisted of the degenerative spondylolisthesis subjects analzed in the historical cohort study (Yuan 1994), which was considered as the control group during classification of pedicle screws to Class II during the 1993 and 1994 Panel meetings as discussed above.

Effectiveness

Although several reports, including randomized prospective studies, have failed to demonstrate improved patient outcomes or fusion rates when instrumented and non-instrumented fusions were compared for treatment of adult isthmic spondylolisthesis

(Thomsen, 1997; McGuire, 1993; Möller, 2000), limitations associated with these investigations included small sample sizes, heterogenous treatment groups, variable clinical outcome measures and non-uniform methods for assessment of radiographic fusion. Kwon (2005) performed a systematic review of surgical literature from 1995-2003 regarding adult low-grade (grades 1 and 2) isthmic spondylolisthesis and compared patients treated with posterolateral fusion (also termed posterior spinal fusion) with or without pedicle fixation, anterior fusion (ALIF or non-instrumented PLIF), and combined procedures (posterior pedicle fixation and interbody fusion (i.e., ALIF, PLIF, TLIF). Patients treated with posterolateral fusion with internal fixation had a significantly higher rate of successful clinical outcomes (84.9%; 304/358) than those treated with uninstrumented fusions (64.4%; 192/298). Patients treated with combined procedures had a higher rate of successful clinical outcomes (86.4%) compared to patients treated with posterior procedures (74.8%). Investigators noted that patients treated with posterolateral fusion with internal fixation experienced significantly higher rates of fusion (90.2%; 333/369) than those who did not receive spinal fixation (77.4%; 254/328), based on covariate analysis. Radiographic outcomes demonstrated a significantly higher fusion rate in patients treated with combined interbody and posterior procedures (98.2% fusion rate, 167/170) compared to patients treated with posterior procedures alone (83.3% fusion rate, 741/890), or anterior stabilization alone (74.0% fusion rate, 57/77).

In the past decade, surgical practice has evolved toward treatment of low-grade spondylolisthesis with posterior interbody fusion techniques (TLIF, PLIF) in combination with pedicle screw spinal systems. Lauber (2006) suggested based on a prospective clinical study that TLIF was safe and effective for treatment of low-grade spondylolisthesis of the isthmic, dysplastic and degenerative types. The radiologic fusion rate was 94.8% overall. Subjects with low-grade isthmic spondylolisthesis had significantly better clinical outcomes than subjects with degenerative spondylolisthesis. Hackenberg (2005) reported a 89% fusion rate and significant improvement in Oswestry Disability Index (ODI) and Visual Analog Scale (VAS) in a prospective study including subjects with low-grade isthmic spondylolisthesis. Subsequently, Wang (2010) prospectively evaluated use of pedicle screw spinal systems in a comparison of minimally invasive TLIF and conventional open TLIF techniques for treatment of grades 1 and 2 isthmic spondylolisthesis and degenerative spondylolisthesis. Fusion rates were similar for both isthmic and degenerative spondylolisthesis groups (97%). Shorter hospitalization and less blood loss were noted in subjects treated with the minimally invasive approach.

Table 5: Effectiveness Data for Posterior Pedicle Screw Spinal Systems for Class III Spondylolisthesis Indications

Author/Year	Group*	Fusion Rate	ODI-Function (pre/last)	VAS Pain-Back (pre/last)
Class III Indications Spondylolisthesis Other Than Grade III-IV at L5-S1 or Degenerative Spondylolisthesis				
Christensen/2002	▪ Non-instrumented PSF ▪ PSF + screws	86% 79%	--	--
Christensen/2002	▪ ASF + PSF + Screws ▪ PSF + screws	92% 80%	-- --	-- --
Hackenberg/2005	TLIF/screws	89%	41.6/23.6	7.6/3.3
Kwon/2005	▪ PSF ± screws ▪ ASF, no screws ▪ Combined ASF + PSF + Screws	83.3% 75.3% 98.2%	--	--
Lauber/2006	TLIF/screws	94.8%	20.05/10.95	7.15/3.6
Bae/2010	▪MIS screws + ALIF, or ▪MIS screws + TLIF	91.3%	52.6%/19.5	7.1/1.9
Kim/2010	MIS Posterior screws + ALIF	100%	54%/27%	6.2/1.7
Kim/2010	▪MIS Posterior screws + ALIF ▪Posterior screws +PSF + ALIF	97.7% 100%	49.3/13.7 60/6.8	7.6/2.1 7.4/1.6
Wang/2010	Screws (conventional and MIS) + TLIF	97.7%	39.9/11.5	7.3/1.0
Park/2011	MIS screws + TLIF	77.3%	60.2/25.9	6.2/2.6
Gerszten/2012	Posterior screws + ALIF rod (presacral)	100%	--	8.1/2.8
Class II Indications – Cohort Study (Degenerative Spondylolisthesis)				
Yuan/1994	PSF + screws	89%	90.4% improved	91.5% improved**

* **PSF** (posterior spinal fusion), **ASF** (anterior spinal fusion, either TLIF, PLIF, ALIF), **Screws** (posterior lumbar pedicle screws), **TLIF** (transforaminal lumbar interbody fusion), **ALIF** (anterior lumbar interbody fusion), **MIS** (minimally invasive surgery technique), **PLIF** (posterior lumbar interbody fusion)
**** Function and pain scores scale:** 1-5 (not ODI or VAS)

Similar high fusion rates (100%) and favorable clinical outcomes have been reported for post-laminectomy spondylolisthesis cases treated with posterior pedicle screw spinal systems in combination with interbody fusion techniques (Hey, 2012). Although studies report high rates of fusion success in severe spondylolisthesis (grades 3 and 4) of the dysplastic type, available literature does not specifically analyze fusion rates for low grade

(grades 1 and 2) dysplastic spondylolisthesis. Literature regarding pathologic spondylolisthesis is limited due to the rare occurrence of this condition, and consists of individual cases series (Lubicky, 2005), which report generally favorable results following treatment with spinal fusion in combination with pedicle fixation systems.

Safety

Recent literature provides evidence to support use of pedicle screw spinal systems as an adjunct to fusion for treatment of spondylolisthesis subtypes currently considered as Class III. Literature demonstrates that use of pedicle screw spinal systems for spondylolisthesis subtypes presently considered as Class III is not associated with additional or more severe risks compared to the risks associated with the use of pedicle screw systems for spondylolisthesis subtypes currently considered as Class II.

In the largest known study regarding adult patients with spondylolisthesis (10,242 total patients, 7,368 degenerative spondylolisthesis patients, 2,608 isthmic spondylolisthesis patients), Sansur (2010) queried the morbidity and mortality database of the Scoliosis Research Society (SRS) to assess the incidence of complications and factors associated with increased complication rates. Surgical treatments were categorized as decompression without fusion, anterior fusion only, combined anterior/posterior fusion, posterior fusion without instrumentation, posterior fusion with instrumentation, and TLIF/PLIF with instrumentation. The most common complications were dural tears (2.1%), wound infections (1.9%), neurological complications (1.1%), and implant complications (0.7%). Deaths occurred in 10 patients (0.1%) and 813 patients experienced complications (7.9%). Notably, the rate of complications was not influenced by surgical approach: decompression without fusion (7.1%), anterior fusion only (7.7%), combined anterior/posterior fusion (7.2%), posterior fusion without instrumentation (7.9%), posterior fusion with instrumentation (8%), and TLIF/PLIF with instrumentation (8%). Data regarding degree of spondylolisthesis was available for 1,767/10,242 (17.3%) of patients. High grade spondylolisthesis (grades 3, 4, and 5) was strongly correlated with a higher rate of complications (22.9% versus 8.3%) compared with low-grade spondylolisthesis (grades 1 and 2) and this finding remained significant following adjustments for age, spondylolithesis type, surgical approach and stratification by revision versus primary procedure. A higher complication rate (8.5%) was associated with degenerative spondylolisthesis compared to isthmic spondylolisthesis (6.6%) and this finding remained significant following adjustment for patient age. The conclusions that can be drawn by the Sansur study are that complications are proportional to the grade of spondylolisthesis such that low-grade non-degenerative spondylolisthesis (Class III indications) had a lower complication rate than severe spondylolisthesis (grades 3 and 4) currently classified as Class II. In addition, comparison of the risk profile regarding use of pedicle screw spinal systems for treatment of subtypes of spondylolisthesis currently considered as Class III are similar to the risks identified for Class II spondylolisthesis indications and are summarized in Table 7.

7.1.3 Safety and Effectiveness: Degenerative Disc Disease

The rationale for use of pedicle fixation in the treatment of DDD relates to the ability of rigid spinal instrumentation to limit strain during the process of fusion healing, thereby enhancing fusion success. The focus of this literature review concerns assessment of

effectiveness (Table 6) and safety (Table 7) of pedicle screw spinal systems for treatment of DDD (Class III indication), as compared to known effectiveness and safety data that exist for other cleared uses of pedicle screw spinal systems as an adjunct to spinal fusion (Class II indications).

Effectiveness

Multiple studies (Zdeblick, 1993; Fischgrund, 1997; Bono, 2004), as well as results of a systematic review by the Cochrane Collaboration (Gibson, 2008), provide evidence to support achievement of higher posterolateral fusion rates with use of pedicle screw spinal systems compared to non-instrumented posterolateral fusions. Regarding use of pedicle screw spinal systems in combination with interbody fusion, results from the Swedish Lumbar Spine Study Group multicenter randomized prospective clinical trial (Fritzell, 2002) demonstrated that the highest fusion rates (91%) were achieved when interbody fusion (either ALIF or PLIF) was performed in combination with posterior pedicle fixation compared to either posterolateral fusion with posterior pedicle screw instrumentation (87%) or non-instrumented posterolateral fusion (72%). The higher fusion rates achieved when interbody fusion was perfomed in conjuction with pedicle screw spinal systems were confirmed by Christensen (2002) in a prospective randomized clinical study, which demonstrated a 92% fusion rate for circumferential fusion in conjunction with pedicle fixation, as compared to an 80% fusion rate for posterolateral fusion performed with pedicle fixation without concomitant interbody fusion. Results from FDA clinical trials support the high rates of fusion success reported when pedicle screw spinal systems are used in conjunction with interbody fusion for treatment of patients with DDD. Brantigan (2000, PMA P960025[4]) reported successful fusion at two years in 98.7% of subjects treated with pedicle screw instrumentation in combination with an interbody fusion device using a PLIF technique.Subsequently, Zigler (2007) reported a 97% rate of successful fusion in subjects with single level DDD treated with ALIF and pedicle screw spinal systems in the control arm of an FDA lumbar disc arthroplasty study (PMA P050010).

Although use of pedicle screw spinal systems in combination with lumbar posterolateral fusion has been associated with higher rates of successful radiographic fusion compared to non-instrumented posterolateral fusion, whether this higher rate of successful fusion is associated with improved clinical outcomes has been debated. In a systematic review by the Cochrane Collaboration (Gibson, 2008), Gibson reported that the improvement in clinical outcomes achieved by use of pedicle fixation in combination with posterolateral fusion was marginal. In contrast, Christensen (2002) reported results from a randomized prospective study with five year follow-up comparing lumbar posterolateral fusion with and without use of adjunctive pedicle fixation, which demonstrated that patients diagnosed with “primary lumbar degeneration” (i.e., no prior surgery), had better back and leg pain outcomes when treated with posterolateral fusion and pedicle screw spinal systems compared with non-instrumented posterolateral fusion. Investigators have attributed the variable outcomes reported following posterolateral fusion with or without pedicle fixation to persistent intervertebral motion and nocioception by inflammatory mediators in the presence of a non-fused disc space at the level where posterior fusion is performed (Weatherly, 1986; Barrick, 2000).

[4] SSED P960025, http://www.accessdata.fda.gov/cdrh_docs/pdf/P960025b.pdf

Studies suggest that addition of some type of interbody fusion (ALIF, TLIF, PLIF) to a procedure involving use of pedicle screw spinal systems and posterolateral fusion result in improved patient outcomes in the population identified as "degenerative disc disease". Videbaek (2006) reported five year follow-up of a randomized trial, which compared treatment with a pedicle screw spinal system in combination with circumferential fusion to treatment with pedicle fixation and posterolateral fusion without concomitant interbody fusion. Results of this trial showed significantly improved clinical outcomes for patients treated with circumferential procedures with respect to pain, general health and disability scores, as judged by validated outcome measures. Hackenberg (2005) investigated outcomes of TLIF performed in conjunction with pedicle fixation and noted that pain reduction (VAS) and functional improvement (ODI) obtained with TLIF in combination with a pedicle screw spinal system were comparable to results reported using ALIF or PLIF techniques. In an FDA approved study (PMA P960025), Brantigan (2000) reported clinical success in 86% of subjects according to FDA study criteria (improvement in pain, maintenance or improvement in neurologic function in terms of motor strength) for patients treated with PLIF using an interbody fusion device and pedicle fixation. Subsequently, Zigler (2007) reported results of single level DDD treated with ALIF and posterior pedicle screw fixation and noted neurologic success (maintenance or improvement in neurologic function) in 81.4%, SF-36 success in 70%, and ODI success ($\geq$ 15% improvement) in 64.8% of subjects in the control arm of an FDA lumbar disc arthroplasty study (PMA P050010).

Interpretation of data regarding effectiveness of a specific surgical intervention in the population category identified as "degenerative disc disease" is limited by the lack of diagnostic specificity for this broad patient group. As noted by Glassman (2009), when subjects identified with DDD are stratified by subgroup according to clinically relevant categories, response to treatment following lumbar fusion varies across diagnostic subgroups. Glassman suggested a framework for stratification into clinically relevant entities, which includes primary surgical cases (disc pathology, spondylolisthesis, instability, stenosis, or scoliosis) and revision surgical cases (nonunion, adjacent level degeneration, or postdiscectomy revision) to improve outcome reporting in future studies relating to lumbar fusion surgery.

During the 1994 classification panel meeting, the reasons for the panel's Class III recommendation for DDD were related to a lack of consensus regarding an appropriate definition for this population, and concerns that clinical results appeared to be device-specific. After several decades of additional clinical use, the literature suggests that a device-specific effect on clinical outcomes is not present, and that mechanical performance as a special control can mitigate potential risks. (See Special Controls Section below.)

The results from the studies considered in this review were compared to the results of the historical cohort study (Yuan 1994), which included an analysis of degenerative spondylolisthesis subjects, and was utilized in support of classification of pedicle screws to Class II for various indications (1993 and 1994 Panel meetings, discussed above. See Section 11 for references).

Table 6: Effectiveness Data for Posterior Pedicle Screw Spinal Systems for Class III Degenerative Indications

Author/Year	Group*	Fusion Rate	ODI-Function (pre/last)	VAS Pain-Back (pre/last)
Class III Indication - Degenerative Disc Disease (DDD)				
Pihlajamaki/1997	PSF + screws	91%	--	--
Brantigan/2000	PLIF + screws	98.7%	--	--
Barnes/2001	PLIF + screws	95%	--	--
Fritzell/2002	PLIF or ALIF + screws PSF + screws	91% 87%	47/39 48/34	66/46 63/40
Christensen/2002	▪ Non-instrumented PSF ▪ PSF + screws	86% 79%	--	--
Christensen/2002	▪ ASF + PSF + Screws ▪ PSF + screws	92% 80%	--	--
Madan/2002	PLIF + screws: With discography Without discography	 -- --	 --/34.2 --/34.2	 --/4.4 --/4.3
Moore/2002	ALIF + screws	95%	--	8.2/5.7
Narayan/2002	PSF + screws	91%	--	--
Brox/2003	PSF + screws	84%	42.0/26.4	62.1/39.4
El-Masry/2004	ALIF + screws	92%	--	--
Hackenberg/2005	TLIF + screws	--	58.4/39	8.3/5.8
Anjarwalla/2006	ALIF + bilateral screws ALIF + unilateral screws	88% 82%	-- --	-- --
Aryan/2007	ALIF + screws	100%	29.7/19.9	8.8/3.9
Sasso/2008	ALIF + screws	--	58/12	82/20
Acosta/2009	Screws + ALIF: ≥65 yrs <65 yrs	 100% 100%	 28.5/19.2 29.7/19.9	 8.7/3.1 8.8/3.9
Arnold/2009	PLIF (with allograft wedge) + screws	98%	--	--
Berg/2009	PLIF or PLF + screws	97%	41.2/23.0	58.5/29.2
Glassman/2009	PSF + screws	--	16.2	2.7
Delamarter/2003 Delamarter 2011	ALIF + screws	--	30.7/14.6 64.8/34.7	6.8/4.0 74.7/38.4
Zigler/2007 Zigler/2012	ALIF + screws	97% 95%	62.7/39.8 --	75/43 --
Class II Indications – Cohort Study (Degenerative Spondylolisthesis)				
Yuan (1994)	PSF + screws	89%	90.4% improved**	91.5% improved**

* **PSF**(posterior spinal fusion), **ASF** (anterior spinal fusion, either TLIF, PLIF, ALIF), **Screws** (posterior lumbar pedicle screws), **TLIF** (transforaminal lumbar interbody fusion), **ALIF**(anterior lumbar interbody fusion), **PLIF**(posterior lumbar interbody fusion), **MIS** (minimally invasive surgery technique)

**** Function and pain scores scale:** 1-5 (not ODI or VAS)

Safety

Based on a survey of literature identified in relation to use of pedicle fixation systems as an adjunct to lumbar fusion for treatment of DDD (Class III indication), the rates for the identified risks to health were similar to the rates reported for existing Class II indications as reported in the cohort study (Yuan, 1994). Similarly, the complication rates reported for spondylolisthesis subtypes currently identified as Class III were similar to the rates reported for spondylolisthesis subtypes presently included in Class II. In addition, the overall complication rates were similar when all Class III indications for use as a group were compared with the Class II cohort (Table 7). Limitations inherent in this analysis are recognized and include variable categorization and reporting of adverse events noted in the literature, use of variable fusion techniques (PLF, ALIF, TLIF, PLIF, MIS), heterogeneity in various treatment groups, variable definitions utilized to determine fusion in the medical literature, and absence of a consensus definition for DDD. When authors could not report complications by indication, the patients were excluded from the analysis.

For all Class III indications considered as a group, complications rates are 1% or less for a majority of events. The events with complication rates higher than 1% include device breakage (1.1%), pseudoarthrosis/failed fusion (4.5%), dural injury (1.6%), wound infection (3.3%), and reoperation including elective implant removal (8.6%) or reoperation not including implant removal (3.8%).

Lower complication rates for the Class III combined cohort compared to the Class II historical cohort were noted for reoperation/removal, screw malposition, failure at the screw/bone interface and dural injury. The rate of reoperation/removal reported for the combined Class III indications cohort are notably lower (8.6% versus 17.6%) when compared to the rates reported in the historical cohort study. In the Class III cohort, the higher rate of reoperation in the Class III DDD group compared to the Class III spondylolisthesis group is attributed to the greater number of elective implant removals noted in the DDD population. The rates of screw malposition, failure at the screw/bone interface (loss of purchase, screw loosening, screw pull-out), and dural injury are all lower for the combined Class III indications cohort compared to the Class II historical cohort. This suggests that complications associated with surgical/operator error have lessened over time as experience related to use of pedicle screw spinal systems has increased across the surgical community.

Higher rates of pseudoarthrosis, device breakage, vascular injury, and infection were noted for the combined Class III indications cohort compared to Class II indications cohort, but these slight differences are not considered to be clinically meaningful. Regarding pseudarthrosis rates (combined Class III indications cohort, 4.5%; Class II indications cohort, 3.7%), these differences are not considered clinically important due to multiple factors including the heterogeneity existing within and between treatment groups, lack of controls for biologic factors that adversely affect fusion success rates, and absence of uniform criteria for assessment of fusion success. Regarding device breakage rates (combined Class III cohort,1.1%; Class II cohort, 0.2%), noted differences are potentially related to the high percentage of patients treated with screw-plate fixation (63%) in the

Class II cohort study compared to Class III patients who were predominantly treated with rod-screw systems. This difference may be related to the inherent mechanical properties of plate versus rod designs, such that the latter implants possess less resistance to bending over the instrumented spinal segments due to the lesser material condition. Vascular injury rates are slightly higher for the combined Class III indications cohort (combined Class III indications cohort, 0.9%; Class II indications cohort, 0.4%), which is anticipated because patients with Class III indications were exposed to the risk of vascular injury as a considerable number of subjects in this group were treated with anterior surgical approaches to the lumbar spine (i.e., ALIF), in contrast to the Class II cohort patients, who were treated predominantly through a posterior surgical approach and were not exposed to the risk of vascular injury. Infection rates differed slightly between patient groups but these differences were not considered clinically meaningful (Combined Class III cohort overall infection rate, 3.3%; superficial infection rate, 0.8%; deep infection rate, 2.2%; Class II cohort overall infection rate: 2.6%).

Table 7: Safety Data for Class III Indications Compared to the Historical Cohort Study

Adverse Events	DDD (Class III Indications) Total: 1350 Complications: 921* Re-operation: 814	Spondylolisthesis (Class III Indications) Total: 506 Complications: 235* Re-operation: 225	Combined Class III Indications Total: 1829 Complications: 1276* Re-operation: 1159	Cohort Study (Class II Indications) Total: 2177 Post-op: 2153
Screw Malposition	0.5%	2.1%	0.9%	1.3%
Screw loosening	0.4%	0.4%	0.5%	5.5%**
Rod/plate/screw breakage	1.3%	0.9%	1.1%	0.2%
Construct Disassembly	0.1%	0.0%	0.1%	0.1%
Bone Fracture	-	-	-	1.9%
Graft Settling/Displacement	0.1%	-	0.2%	-
Pseudoarthrosis	5.9%	0.2%	4.5%	3.7%
Bleeding/Vascular Injury	0.7%	2.6%	0.9%	0.4%
Neurologic Injury	0.8%	0.9%	0.6%	0.8%
nerve root injury	*0.3%*		*0.3%*	*0.4%*
spinal cord injury	*0.0%*		*0.0%*	*0.3%*
Back/Leg Pain (Radiculopathy)	0.7%	0.4%	0.7%	0.9% unspecified 1.5% permanent 3.5% transient
Dural Tear/CSF Leak	1.0%	-	1.6%	7.4%/0.5%
Wound problems *(hematoma/seroma)*	0.3%	1.3%	0.5%	-
Infection/Sepsis	3.9%	0.9%	3.3%	2.6%
Superficial	*2.6%*	-	*2.2%*	
Deep	*0.9%*	*0.9%*	*0.8%*	
Skin Irritation	0.3%	-	0.2%	-
Cardiac	0.2%	-	0.2%	-
Respiratory	0.4%	-	0.4%	-
Gastrointestinal	0.3%	-	0.2%	-
Urologic/Reproductive	0.1%	-	0.1%	-
Reoperation/Revision	10.9%	3.6%	8.6%	17.6%
Removal of hardware	*5.5%*	*1.3%*	*3.8%*	*12.5%*

* The total number of patients included in the analysis of complications does not include patients in publications where the complications were not reported by indication (e.g., Class II degenerative spondylolisthesis from Class III isthmic spondylolisthesis).

**Screw Malposition: include screw breakout and vertebral body penetration

***Screw loosening: includes loss of purchase, screw loosening, and screw pull out

7.1.4 Conclusions: Targeted Literature Search

In conclusion, the clinical evidence appears to support a reasonable assurance of safety and effectiveness for pedicle screw spinal systems used in isolation, or in combination with interbody fusion, for treatment of degenerative disc disease and spondylolisthesis other than either severe spondylolisthesis (grades 3 and 4) at L5-S1 or degenerative spondylolisthesis with objective evidence of neurologic impairment.

7.2 Office of Surveillance and Biometrics Systematic Literature Search for DDD

While conscious of the limitations identified above regarding precision of definitions for DDD, the FDA's Office of Surveillance and Biometrics (OSB) conducted a systematic literature search published from 1990- present. The purpose of this literature search is to examine the evidence to summarize (i) the fusion rates for pedicle screw instrumentation in patients with DDD and, (ii) reported adverse events associated with pedicle screw instrumentation for DDD. This study confirms the conclusions of the targeted literature search. In addition, this literature search captured additional techniques recognized as off-label, but known to be used clinically in posterior spinal fusion, such as use of alternative graft materials within a cage.

7.2.1 Methods

A systematic search of the published peer-reviewed literature was conducted on February 7th, 2013 using the PubMed database. The search strategy and inclusion and exclusion criteria are summarized in Figure 1 below.

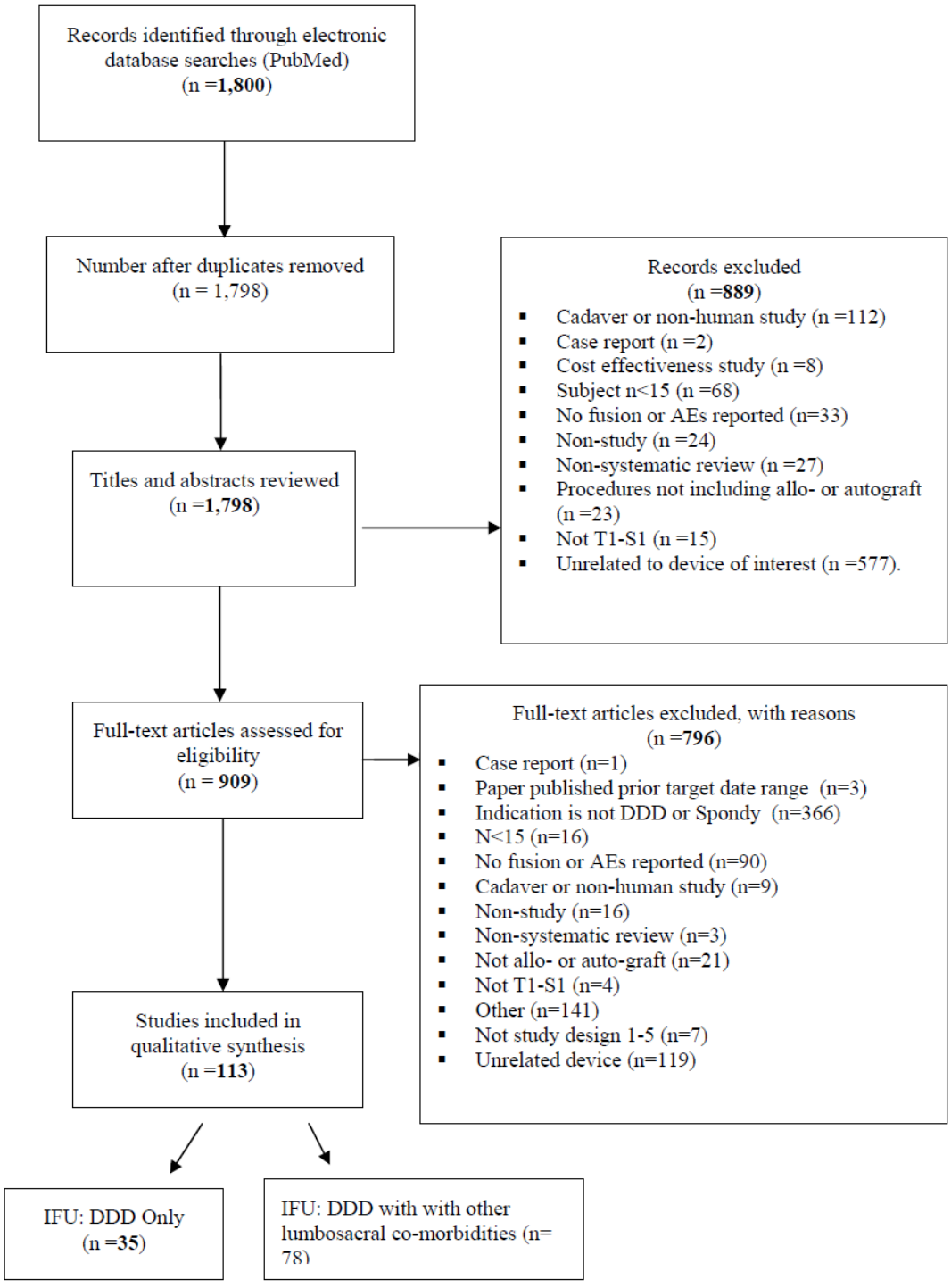

Figure 1: Flow diagram of article retrieval and selection

7.2.2 Results

This systematic literature search of pedicle instrumentation in patients with DDD includes 31 primary research articles (9 randomized controlled trials and 22 observational studies)

as well as one meta-analyses and three systematic reviews. Of the 31 primary research articles, 17 were from United States. The range for the follow-up in the selected publications was 6 months to 96 months.

In the 31 primary research articles, the range for the age mean was 36 to 74 years across the publications, with the absolute range of 15-85 years old. Out of these, twenty-seven studies included adult population only (≥21 years old, per FDA/CDRH pediatric definition). In the studies where a mixed population was noted, none of the authors stated that skeletally immature patients were included in the study. Thus all patients in the included papers were considered skeletally mature for the purpose of this review.

Effectiveness (DDD):
The effectiveness of the pedicle screw instrumentation was evaluated based on the fusion rate as reported by the authors. The fusion was measured as proportion of patients out of the total sample for each investigation who were deemed to have successful fusion or union. 29 (N=3108) of the 35 studies reported fusion rate for the unique population. In addition, 2 of these studies included a mixed patient indication and reported fusion rate separately for the DDD patients only (Zdeblick, 1993; Finkenberg, 2001).

Of the 29 studies, the fusion rate ranged from 67-100%. Of note, Zdeblick and colleagues reported fusion rates for 3 subgroups (group 3 – rigid fixation; group 2 – nonrigid fixation; group 1 – non-instrumented). In Zdeblick's and colleagues' investigation, the fusion rate with use of a rigid pedicle screw spinal system was 93%, whereas the two sub-groups with lower fusion rates (45-67%) were treated either without the use of adjunctive fixation or were treated using a semi-rigid pedicle screw/plate system which is no longer representative of current rigid systems. When patients treated with semi-rigid fixation were excluded, the overall fusion rates in the evaluated literature ranged from 76.9-100%. Also, for studies where endpoints were reported by surgical approach, fusion rates were consistent across varying surgical approachs (PSF, PLIF, TLIF, ALIF, circumferential fusion) and were within the overall range. See Table 8.

Table 8: Pedicle Screw Instrumented Fusion by Anatomical Approach

Author	Year	N	Fusion rate
Anjarwalla NK	2006	81	ALIF: unilateral pedicle (82%), bilateral pedicle (87%)
Audat Z	2012	81	PSF 88%, PLIF 88.9% and TLIF 91.9%
Faundez AA	2009	133	APF: 82.4%; TLIF: 76.9%
Kim KT	2006	167	PSF: 92%; PLIF: 95%; PSF+PLIF: 96%
Madan SS	2003	74	ALIF: 100%; PLIF: 94.3%
Madan SS	2003	71	PSF: 95.5%; PLIF: 100%

ALIF- Anterior lumbar interbody fusion, APF- Anterior/posterior spine fusion (circumferential fusion), TLIF- Transforaminal lumbar interbody fusion, PLF- Posterior spinal fusion (posterolateral fusion), PLIF- posterior lumbar interbody fusion

Safety (DDD)
The safety of the pedicle screw instrumentation was evaluated based on the reported adverse events (AE) during the surgery and postoperatively. Thirty (31) of the 32 primary research articles and one meta-analyses reported information on the AE events.

The reported AE events were:

- revision and reoperations
- pain
- neurological complications
- urinary tract infections
- superficial and deep wound infections
- postoperative pneumonia
- retrograde ejaculation
- excessive intra-operative bleeding
- other cardiovascular events (e.g. venous thrombosis, pulmonary embolism)
- dural tear.

Reproductive/Gastrointestinal events such as urinary tract infections and retrograde ejaculation are more likely associated with an anterior approach to place an interbody device, which may occur in the same surgical procedure as placement of posterior pedicle screw spinal systems. Postoperative pneumonia is a general surgical/anesthesia risk and is not associated with pedicle screw spinal system placement. The other events are consistent with the risks to health identified via the targeted literature search. See Table 7.

The OSB literature review reported a range of rates for each event, calculated within each study. This method differs from the targeted literature search analysis which totals the number of events over all patients included in the analysis. Thus the rates reported here are slightly higher than those reported in Table 7.

Seventeen (17) publications reported information on the revisions and reoperations. Revision was reported in 11 publications. Overall range for the revisions was 0-37.5%, out of which 7 publications reported revision rate below 10%. The most frequently reported reasons for revision were pain and pseudoathrosis. Two (2) articles in this review reported a rate pedicle screw removals due to persistent pain above 20% (Berg, 2009; Fogel, 2009). Potential reasons for these high rates include potential investigator bias (Berg) or a high percentage of patients offered removal of hardware despite successful fusion (Fogel).

Fourteen (14) investigations provided information on infection rate. Overall the post-operative infection rate ranged from 0-7.4%. Thirteen (13) articles provided information on neurological complications such as sciatica, dorsiflexion, weakness in ankle/foot-drop, nerve palsy, root-damage, and etc). The range for the neurological complications was 0-14.8%. Audat (2012) reported 14.8% (12/81) neurological complications. However, according to the authors “most of these complications were resolved with proper management, and only foot drop persisted” in 3 patients. Without taking into account this investigation the range for neurological complications was 0-5.8%.

7.2.3 Discussion- OSB Systematic Literature Search

This systematic review included 35 publications on the pedicle screw instrumented fusion in DDD patients. In the 34 of the 35 studies, the reported lumbar fusion rates performed via pedicle screws in skeletally mature patients with DDD were above 80%. Moreover, the one publication that reported fusion success below 80% had low quality of evidence due to small sample size in the sub-group (n=14) and this sub-group also was instrumented with a semi-rigid plate and screw system.

In 17 of 32 articles with reported AE events, the described AE events included revisions/reoperations, infections and neurological complications. Pedicle screw removal, after successful fusion, due to pain was the most common reason for post-op surgical intervention. Adjacent segment pathology was the most frequently cited reason for the re-operations.

However, the findings of the present systematic review are limited due to the following constraints in the methodology of the selected publications and current review.

- This review did not employ a clearly operationalized definition for the DDD and rather relied on the investigators determination. It is likely that patient heterogeneity in terms of their clinical status may contribute to inaccuracy of the estimates of the pedicle screw assisted lumbar fusion rates and adverse events rates in the DDD patients. Given that minimal information is available for robust estimates of lumbar fusion rates and adverse events rates for other lumbosacral co-morbidities, it remains unclear if potential patient heterogeneity would contribute to underestimation or overestimation of the fusion rates and AE rates in DDD patients.
- There was high variability in the definitions for the re-operations and revision across selected investigations. For example, some authors would use both interchangeably, while others would define revision as failure of the surgery for the indicated levels (e.g. failed fusion, device malfunction, pain) and re-operation as complications (e.g. adjacent segment pathology) which do not involve index segments or are due to worsening of the clinical pathology. This discrepancy in the use of the terminology and definitions may lead to inaccurate evaluation of the pedicle screw instrumented fusion in the DDD patients.
- This review did not use any particular definition for what should constitute successful fusion and, similarly to the DDD determination, relied on the investigators' determinations. This misclassification of study outcomes may limit comparisons of lumbar rates across publications and thus, limit the inferences about pedicle screw instrumented fusion in the DDD patients.
- Other limitations include small sample size in the majority of the publications (n<50), lack of uniformity in the patient characteristics (age, illness and its severity), and treatment (different constructs, number of screws, number of levels treated).
- In addition, due to the high variability in the patient characteristics, surgical approach and technique, number of levels treated, it is not feasible to make definite observations in terms of the factors (e.g. age, level of fusion, clinical condition) which *might* be related to the safety and effectiveness of cervical screw use in DDD population.

Recent publications (Phillips, 2013) corroborate these limitations of systematic searches in this population. However, despite the limitations in the patient population and the application of the definitions of DDD, fusion, and AEs, the conclusions reached in this systematic literature review parallel those found in the targeted literature review discussed in Section 7.1.

7.3 Dynamic Stabilization

The scope of Section7.1 and Section 7.2 above is limited to pedicle screw spinal systems under 21 CFR 888.3070 that provide traditional, rigid stabilization as an adjunct to fusion. These systems have a long history of clinical use, and have been legally marketed for decades.

A specific subtype of pedicle screw spinal systems, namely dynamic stabilization systems, provides "semi-rigid" fixation through various design features (e.g., polymer cords, moveable screw heads, and springs) that allow bending or rotation. Since 1997, 16 dynamic stabilization systems, when intended to be used as an adjunct to fusion, were determined to be substantially equivalent (SE) to traditional pedicle screw spinal systems on the basis of comparative mechanical testing, and cleared through the 510(k) regulatory process. Some of these systems have both Class II and Class III indications for use.

FDA became aware of clinical failures that were not predicted by the current special controls (mechanical testing) pertaining to pedicle screw spinal systems, including one recall of a dynamic stabilization system. As a result, FDA issued post-market surveillance orders for all dynamic stabilization systems cleared through the 510(k) regulatory process as an adjunct to fusion on October 5, 2009, under authority provided by Section 522 of the Act, 21 U.S.C. 360l. The purpose of these "522 Orders" is to collect clinical data on a number of potential safety issues, including fusion rates and frequency of additional surgeries. Affected manufacturers were required: 1) to conduct post-market surveillance on the fusion rates, adverse events, and subsequent surgical procedures of their dynamic stabilization system, as compared to traditional pedicle screw spinal systems; and 2) to conduct formal explant analyses, when applicable.

As of March 2013, out of the 16 522 Orders, 3 are pending, 3 have inadequate progress, 1 has been terminated, and 9 are categorized as 'Other' (reasons may include that the manufacturer is no longer marketing their device). Furthermore, there is limited safety and effectiveness data in the literature for dynamic stabilization systems when used as an adjunct to fusion (see Appendix B). The limited information from the Medical Device Report (MDR) search described in Section 7.4 below may suggest a higher rate of serious adverse events (device breakage, pain, and reoperation) compared to traditional rigid systems. However, due to the small amount of published literature on these devices, FDA believes that the safety and effectiveness profile for dynamic stabilization systems is not well established for this device subtype. Therefore, at this time, we do not believe that the special controls utilized for traditional rigid systems are appropriate to mitigate the risks to health for dynamic stabilization systems.

The panel will be asked to comment on the appropriate classification for dynamic stabilization systems based on the scientific evidence available to demonstrate a reasonable assurance of safety and effectiveness for use of these devices as an adjunct to fusion. Additionally, the panel will be asked to comment on the risks to health posed by dynamic stabilization systems, and whether or not special controls can be developed for this device subtype. We will also be asking you to comment on what design features constitute a dynamic stabilization system intended as an adjunct to fusion.

7.4 Adverse Events Associated with Thoracolumbosacral Pedicle Screw Fixation

7.4.1 Search Methodology

Medical Device Reporting (MDR) is the mechanism for the FDA to receive significant medical device adverse events from manufacturers, importers and user facilities. Information is gathered via the use of prespecified codes (patient or device problem codes) as well as a user narrative of the event. This search was conducted to identify the types of adverse events reported for pedicle screw spinal systems. Multiple queries were created to identify all relevant MDRs from the Manufacturer and User Facility Device Experience (MAUDE) Database. The searches were run by product code and date entered. The search was limited to reports received between January 1, 2003 and December 31, 2012.

A total of 6,595 unique MDRs were found related to the product codes associated with pedicle screw spinal systems. The reports are separated by product codes for comparison based on how they are used:

- NKB represents the Class III indication of DDD and other types of spondylolisthesis other than severe spondylolisthesis (grades 3 or 4) or degenerative spondylolisthesis with objective evidence of neurologic impairment;
- MNH and MNI are used for pedicle screw fixation Class II uses;
- NQP is used for dynamic stabilization systems (DSS);
- OSH is a newer product code for adolescent idiopathic scoliosis (AIS); and
- KWP is used for posterior, non-pedicle based components (e.g., hooks, spinous process plates), but these components are often included as part of pedicle screw spinal systems.

See Appendix C for details of how these results were analyzed.

7.4.2 Results: Adverse Event Information

The types of adverse events are displayed in Table 9. These are based on the device and patient problem codes associated with each MDR. The corresponding rate is calculated as the incidence of each event out of the total number of reports for each product code. The total number of device uses under each product code is unknown. All codes with a greater than one percent incidence within their product code grouping are shown. Note that a single MDR may be associated with more than one problem code. Further, the lack of a device or patient problem code in an MDR does not necessarily signify a specific adverse event type did not occur.

Table 9: Incidence of Adverse Events as Reported in MAUDE (by Product Code)

Adverse event	Percentage of incidence within product code group				
	NKB (N=1733)	MNH/MNI (N=1138)	KWP (N=3260)	NQP (N=463)	OSH (N=1)
Malpositioned device/Surgeon error	9.5%	10.8%	17.2%	--	--
Device disassembly	40.2%	45.5%	34.2%	9.7%	--
Device breakage	31%	34.9%	39%	59.8%	100%
Device malfunction	5.3%	5.1%	2.5%	2.6%	100%
Surrounding bone issues	3.7%	1.7%	101%	--	--
Infection	1.7%	1.8%	2%	1.9%	--
Pain	12.6%	14.7%	13.7%	27.2%	--
Fall	1.2%	1.7%	1%	1.9%	--
Additional procedures necessary	4.2%	34.1%	29.8%	46.9%	--
Device removal	5.6%	32.2%	28.5%	12.1%	--
Not specified (device codes)	9.6%	4.4%	6.7%	9.3%	--
Not specified (patient codes)	65%	50.2%	49.6%	35.4%	--

Device and patient problem codes were not provided in all MDRs. The percentages of reports without any associated codes are shown in Table 10.

Table 10: Percentages of MDR reports without problem codes

No problem codes provided	Percentage of reports within product code group				
	NKB (N=1733)	MNH/MNI (N=1138)	KWP (N=3260)	NQP (N=463)	OSH (N=1)
Device problem codes	16.5%	12%	5.8%	7.1%	0%
Patient problem codes	0.2%	0.2%	0.2%	0.4%	0%

7.4.3 Discussion: NKB vs. MNH/MNI

The adverse event types provided by the device and patient problem codes are similar between NKB and MNH/MNI. Noted differences are only seen in two categories, Additional procedures necessary and Device removal, where MNH/MNI is greater by nearly 30% in each. It is likely this difference can be attributed to lack of reporting the problem codes under NKB that correspond to these categories. To support this, a text search was performed on the event texts of the NKB reports with the term ‘revis’ (to capture variations of revision and correspond to the category Additional procedures necessary). In the 1,733 MDRs, 669 contained ‘revis’, for a 38.6% incidence. This matches much more closely to the 34.1% in MNH/MNI. Corresponding to Device removal, the term ‘remov’ was used in a text search and was identified in 756 MDRs (43.6%), closer to the 32.2% in MNH/MNI.

The time from implantation to occurrence of the adverse event is similar across all product codes; the highest number is seen within the second year after implantation. Adverse events are often reported at or before the two year timepoint, when clinical decisions are made regarding the fusion status of the construct. In the absence of adequate fusion, implants

may be expected to fail due to exposure to extended fatigue loads. The similar trend in time to event may suggest that the time to failure for these devices is not dependent on the different indications for which these devices were used.

Patient demographics (age, gender, and weight) follow similar trends across all product codes, with the exception of OSH, which only contained a single report without any patient information. The demographic similarities indicate similar patient populations for devices that fall under these product codes. However, it should be noted that the specific reason for treatment (e.g., DDD, fracture, scoliosis) was not provided in the MDRs.

The limitations inherent in the use of product codes in this regulation preclude an exact analysis of the data. As noted above, the product code reported for an event may not correspond to the indication that was treated. In addition the report codes may have been used incorrectly or inconsistently. Report codes were used for the analysis in order to eliminate bias associated with text searches.

The incidence and types of adverse events reported under product code NKB fall within the scope of those reported under the Class II product codes for pedicle screw spinal systems-MNI/MNH and KWP.

7.4.4 Discussion: NQP Dynamic Stabilization

Overall numbers of adverse events are lower in this category due to the limited use and distribution of these devices. However, of note, the incidence of device breakage, pain, and additional procedures necessary are higher in the NQP product code than any other product code used for pedicle screw spinal systems.

7.5 Summary of Clinical Evidence

Based upon the clinical evidence reviewed by FDA (and provided by OSMA in their response to the 515(i) Order), as well as the MDR search described above, it appears that there is a reasonable assurance of safety and effectiveness for traditional, rigid pedicle screw spinal systems when used for current class III indications (i.e., DDD and types of spondylolisthesis other than severe spondylolisthesis (grades 3 or 4) or degenerative spondylolisthesis with objective evidence of neurologic impairment).

FDA believes that the safety and effectiveness profile for DSSs are not currently well established, so special controls cannot be developed at this time to mitigate the risks to health.

The panel will be asked whether the evidence demonstrates a reasonable assurance of safety and effectiveness for the indications for use described above in both:

- ***Traditional, rigid pedicle screw spinal systems***
- ***Dynamic stabilization systems used as an adunct to fusion.***

8. Discussion of Risks to Health

8.1 1994 Classification Panel – Identified Risks to Health

The specific risks identified in relation to pedicle screw spinal systems at the 1994 panel meeting were:

- Device Related Risks
  - Hardware breakage (including screw breakage)
  - Implant loosening
  - Loss of screw purchase
  - Pedicle fracture
  - Canal or root impingement
  - Dural tears
  - Failure to heal
  - Pseudarthrosis
  - Reoperation

- Operative Risks
  - Poor screw placement
  - Blind application
  - Surgical technique or judgment error
  - Steep learning curve for new users
  - Infection
  - Bleeding/vascular injury
  - Nerve damage

8.2 Updated Risks to Health

Since the 1994 panel meeting, considerably more is known regarding the risk profile of pedicle screw spinal systems. In considering risks to health, the FDA has evaluated the available clinical evidence in the published literature; the device related adverse events reported in the FDA MAUDE database; and the risks identified by the manufacturers who responded to the 515(i) Order. The current risks to health identified through the sources above include the following:

- Malposition
- Implant Loosening
- Device Breakage
- Device Malfunction
- Disassembly
- Bone Fracture
- Graft Settling/Displacement
- Loss of Correction
- Pseudoarthrosis
- Bleeding/Vascular Injury
- Neurologic Injury
- Back/Leg Pain
- Dural Injury/CSF Leak

- Wound Problems
- Infection/Sepsis
- Skin Irritation
- Cardiac
- Respiratory
- Gastrointestinal
- Revision Surgery
- Death

In general, the FDA agrees with the risks proposed in the responses to the 515(i) Order with the exception of the following risks, which FDA does not concur are applicable to pedicle screw spinal system use:

- Identification of urologic/reproductive risks as a potential risk of using posterior pedicle screws. FDA believes that these events are associated with anterior approaches, which may be done concomitantly with posterior pedicle screw fixation, but do not occur as a result of pedicle screw spinal system placement.
- Identification of "Extended Surgery Time" as a new risk to health. While this may be considered an individual event, extended surgery time may be due to or may result in complications that are already in the risks listed above, and is considered a general surgical risk rather than a risk specific to the use of pedicle screw spinal systems.
- Identification of "herniated nucleus pulposus" as a new risk to health. Herniated nucleus pulposis at a treated level is not a risk likely to be associated with use of pedicle screw spinal systems intended as an adjunct to fusion.
- Identification of "pediatric, loss of growth" as an additional risk. This risk is addressed by prior classification of pediatric use of pedicle screws (see Section 4 and Appendix A), and is outside the scope of this current classification discussion related to Class III indications for pedicle screw spinal systems.

FDA agrees with the following risks identified in the responses to the 515(i) Order, but consider these risks to be associated within a broader category of risks to health, as follows:

- The risk of "nonunion" is already covered under the broader heading of 'pseudoarthrosis."
- The events associated with "Foreign Body Reaction" may already be covered under the broader headings of "implant loosening" or "skin irritation."

The panel will be asked to comment on the risks to health identified and whether there are additional risks that should be considered for pedicle screw spinal systems used in the thoracolumbosacral spine for treatment of DDD and spondylolisthesis (other than severe spondylolisthesis (grades 3 or 4) or degenerative spondylolisthesis with objective evidence of neurologic impairment). The panel will also be asked to comment on whether there are additional risks to health associated with DSSs.

9. Mitigation of Risks to Health

9.1 Overview of Proposed Special Controls

Based on the safety and effectiveness information provided in the responses to the 515(i) Order, as well as information gathered by the FDA, FDA believes that for the remaining class III indications for traditional, rigid pedicle screw spinal systems, special controls can be developed to adequately mitigate the risks to health described in Section 8.2 above.

The following special controls are proposed and discussed further in the sections below:

- Labeling - *must bear all information required for the safe and effective use of the device as outlined in 21 CFR 801.109(c).*
- Biocompatibility - *material characterization, including conformance to material standards, must demonstrate biocompatibility of the device materials and any potential byproducts (e.g., wear debris, leachates, etc).*
- Sterility - *validation must demonstrate the sterility of, or the ability to sterilize, the device components.*
- Mechanical testing - *non-clinical performance testing must demonstrate the mechanical function and durability of the device components.*

When evaluating the adequacy of the special controls, it is important to understand that the FDA correlates the ability of each special control identified to mitigate an identified risk to health.

9.1.1 Labeling

The following labeling special controls are proposed in OSMA's response to the 515(i) Order:

- "Precaution: The implantation of pedicle screw spinal systems should be performed only by experienced spinal surgeons with specific training in the use of pedicle screw spinal systems."
- Labeling requirements presented in FDA guidance documents, including the *Device Labeling Guidance (#G91-1 (Blue Book Memo))*, which describes the contents of the label including indications, contraindications, precautions and warnings.

Additionally, OSMA's response to the 515(i) Order as well as the response from Pioneer Surgical Technology propose elimination of the following warning from 21 CFR 888.3070 as this warning may no longer be accurate:

- "Warning: The safety and effectiveness of pedicle screw spinal systems have been established only for spinal conditions with significant mechanical instability or deformity requiring fusion with instrumentation. These conditions are significant mechanical instability or deformity of the thoracic, lumbar, and sacral spine secondary to severe spondylolisthesis (grades 3 and 4) of the L5-S1 vertebra, degenerative spondylolisthesis with objective evidence of neurologic impairment, fracture, dislocation, scoliosis, kyphosis, spinal tumor, and failed previous fusion

(pseudoarthrosis). The safety and effectiveness of these devices for any other conditions are unknown."

The panel will be asked to comment on whether inclusion or removal of the aforementioned warnings is appropriate, given that there is additional clinical data since the creation of the original pedicle screw classification regulation.

9.1.2 Biocompatibility

Multiple responses to the 515(i) order referenced ISO 10993: Biological Evaluation of Medical Devices as a method to assess biocompatibility of alternative or new materials. Additionally, multiple responses to the 515(i) Order proposed compliance with material standards. FDA often relies on standards published through organizations like ASTM International and the International Standards Organization (ISO), in order to provide standard guides and methods for characterizing and testing medical devices. The FDA Modernization Act of 1997 (FDAMA) (Pub. L. 105-115) amended section 514 of the Act to specifically authorize the FDA to recognize all or part of national and international standards as consensus standards for utilization by the Center for Devices and Radiological Health (CDRH). These standards can then be used across numerous manufacturers as a means for meaningful device comparison in 510(k) submissions for the purpose of establishing substantial equivalence (SE).

The following standards were specifically referenced in OSMA's response to the 515(i) Order as the standard specifications to which materials when used to manufacture posterior pedicle screws should comply:

- **ASTM F138-08** – Standard Specification for Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless Steel Bar and Wire for Surgical Implants
- **ASTM F67-06** – Standard Specification for Unalloyed Titanium, for Surgical Implant Applications
- **ASTM F1537-08** – Standard Specification for Wrought Cobalt-28Chromium-6Molybdenum Alloys for Surgical Implants
- **ASTM F136-08e1** – Standard Specification for Wrought Titanium-6Aluminum-4Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications
- **ASTM F1295** – Standard Specification for Wrought Titanium-6 Aluminum-7 Niobium Alloy for Surgical Implant Applications
- **ASTM F2063**-05 – Standard Specification for Wrought Nickel-Titanium Shape Memory Alloys for Medical Devices and Surgical Implants

9.1.3 Sterility

As outlined in the response to the 515(i) Order from Globus Medical, sterilization validation testing must demonstrate the sterility of, or the ability to sterilize, the device components and any associated instruments with a sterility assurance level (SAL) of 1×10^{-6} using a sterilization cycle that has been validated in accordance with the quality system regulation (21 CFR Part 820).

9.1.4 Mechanical Testing

In vitro mechanical testing is recommended as a special control to mitigate some of the risks to health associated with the performance of these devices. As presented in multiple responses to the 515(i) Order, there are multiple existing standards that outline methods for mechanical testing of the pedicle screw spinal systems that FDA believes are applicable and appropriate to mitigate some of the identified risks to health. OSMA's response to the 515(i) order specifically mentions the following two test standards:

- **ASTM F1717**
  ASTM F1717: *Standard Test Methods for Spinal Implant Constructs in a Vertebrectomy Model*, discusses test methods for evaluating whole spinal constructs. Thoracolumbosacral pedicle screw spinal systems for use as an adjunct to fusion, regardless of Class II or Class III indications for use, have been subjected to mechanical evaluation utilizing this standard since May 3, 2004 as outlined in the Spinal Systems 510(k) Guidance.
- **ASTM F1798**
  In addition, ASTM F1798: *Standard Guide for Evaluating Static and Fatigue Properties of Interconnection Mechanisms and Subassemblies Used in Spinal Arthrodesis Implants*, discusses various ways to test spinal device components, specifically the interconnection mechanism between these components. The FDA considers ASTM F1798 to be particularly useful for evaluating modifications to subcomponents in spinal systems. Examples of components tested in combination are screws, hooks, and rods.

The FDA may request other mechanical testing not listed in these standards or a guidance document (e.g., wear characterization), depending on the technological characteristics of the spinal system.

9.2 Mitigation of Risks to Health

The list of risks provided in Table 11, compiled from the responses to the 515(i) Order, outlines whether the special controls are adequate to mitigate each risk to health associated with pedicle screw spinal systems identified above in Section 8.2.

Table 11: Risks and Associated Mitigation Activities

Identified Risk	Recommended Mitigation Measures			
	Mechanical Testing	Biocompatibility	Labeling	Sterility
Malposition			Yes	
Implant Loosening	Yes	Yes	Yes	
Device Breakage	Yes		Yes	
Disassembly	Yes		Yes	
Bone Fracture			Yes	
Graft Settling/ Displacement			Yes	
Loss of Correction	Yes		Yes	
Pseudarthrosis	Yes	Yes	Yes	
Bleeding/Vascular Injury			Yes	
Neurologic Injury			Yes	
Dural Injury/CSF Leak			Yes	
Wound			Yes	
Infection/Sepsis			Yes	Yes
Skin Irritation		Yes	Yes	
Cardiac			Yes	
Back/leg pain			Yes	
Gastrointestinal			Yes	
Respiratory			Yes	
Revision Surgery	Yes	Yes	Yes	Yes
Death	Yes	Yes	Yes	Yes

FDA agrees with the mitigation activities associated with the identified risks to health proposed in the responses to the 515(i) Order, with the exception of:

- Identification of mechanical testing as a special control to mitigate the risk of implant loosening (loss of fixation). The recognized standards currently in use to

evaluate mechanical performance in a non-clinical setting are not designed to simulate the implant/bone interface.

The panel will be asked to comment on the adequacy of the proposed special controls to mitigate the risks to health for traditional, rigid pedicle screw spinal systems.

10. Device Classification

For the purposes of classification (see the Regulatory Reference Sheet for additional information), FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. the persons for whose use the device is represented or intended;
2. the conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;
3. the probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. the reliability of the device.

Part (g)(1) of this regulation further states that it "is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is **reasonable assurance of the safety and effectiveness** of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into class III."

Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use."

Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e)(1), "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

FDA believes that the available scientific evidence supports a Class II determination for the use of pedicle screw spinal systems in the treatment of DDD and spondylolisthesis other than either severe spondylolisthesis (grades 3 and 4) at L5-S1 or degenerative spondylolisthesis with objective evidence of neurologic impairment. The available evidence supports a reasonable assurance of safety and effectiveness, the proposed special controls would be sufficient to provide such assurance, and there is not an unreasonable risk of illness or injury for the traditional, rigid pedicle screw spinal systems.

The panel will be asked to comment on the proposed device classification for traditional, rigid pedicle screw spinal systems, as well as dynamic stabilization systems.

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12. Appendix A: Regulatory History of Pediatric Uses

To support the assertion that pediatric pedicle screw uses of thoracolumbosacral pedicle screw spinal systems have been classified via the 510(k) process, which opposes the 2001 technical amendment, the regulatory history of pediatric pedicle screw use is outlined below.

Table 1: History of pedicle screw clearances for pediatric and skeletally immature patients

Date	Description	510(k) Cleared Indication
1996	First clearances for downsized rods, hooks, and screws intended for use in the lumbar spine for pediatric and other applications where anatomic considerations limit the size of the implants that can be used for internal fixation applications	When labeled for pedicle screw fixation, the [system] components are intended for ***use in grade 3 or 4 spondylolisthesis at L5-S1*** using autologous bone graft and intended to be removed after solid fusion is obtained.
1998	First consideration of mechanical requirements for reduced body weight of pediatric patients	When labeled for pedicle screw fixation, the [system] is intended for use in ***grade 3 or 4 spondylolisthesis at the fifth lumbar- first sacral vertebra joint (L5-S1)*** utilizing autologous bone graft and intended to be removed after solid fusion is attained. ***The [system] is intended for pediatric patients with a body weight of 50lbs or less.***
1999	Addition of pediatric patients and skeletally mature patients of small stature	…In addition the [system] is intended for treatment of severe spondylolisthesis grade 3 and 4 of the L5-S1 vertebra in skeletally mature patients (including small stature) ***and pediatric*** patients receiving fusion by autogenous bone graft…
2003	Inclusion of thoracic uses for skeletally immature patients made through exclusion of a system from the skeletally mature requirement	Pedicle screw fixation is ***limited to skeletally mature patients with the exception of the [system].*** These devices are indicated for all of the following indications regardless of the intended use:
2007	Specific clearance for pediatric scoliosis, silent on skeletal maturity	posterior, non-cervical pedicle screw system indicated to treat ***pediatric scoliosis*** by (1) correction, (2) stabilization, (3) adjustment and (4) fixation of the scoliotic spine.
2009	Specific clearance for Adolescent Idiopathic Scoliosis, which may be a skeletally mature or immature population	When used for posterior non-cervical pedicle screw fixation in pediatric patients, the [system] implants are indicated as an adjunct to fusion to treat ***adolescent idiopathic scoliosis.***
2011	Specific clearance for spondylolisthesis/spondylolysis, and fracture caused by tumor or trauma in pediatric patients	The [system] is intended to treat ***pediatric patients*** diagnosed with the following conditions: spondylolisthesis; fracture/dislocation; and/or trauma

Clinical Rationale:

Treatment of adolescent idiopathic scoliosis (AIS) using pedicle screw spinal systems can be considered worst-case compared to other pediatric spinal conditions in terms of biomechanical demands on the implant system. As many AIS patients are approaching or have achieved full skeletal maturity, the spinal implant constructs in these patients are expected to sustain the similar patterns of loading as adult patients. In addition, AIS curves are often challenging to instrument and require application of significant corrective forces to realign severe spinal curvatures. When this population is treated with definitive fusion, this use is already considered a Class II indication, per the above regulatory history. However, the AIS population is heterogeneous with respect to attainment of skeletal maturity, as this population contains skeletally immature patients, as well as patients who are approaching or have previously achieved skeletal maturity.

In addition, there exists extensive literature (including data from meta-analysis, systematic literature reviews, literature case series and spine specialty society databases) documenting the safety and effectiveness of pedicle screws in the thoracolumbosacral spine in pediatric patients for fusion indications (Ledonio, 2011; Lykissas, 2013; Reames 2011; Ruf 2002). The most extensive data exists related to screw use in the pediatric spinal deformity population, with the largest groups consisting of patients with idiopathic scoliosis and spondylolisthesis. This cumulative literature experience indicates that the use of pedicle screws is associated with greater Cobb angle correction, as compared with alternative spinal anchors including hook constructs and hybrid constructs (combinations of hooks, wires, and screws). There exists documented clinical experience demonstrating the safe and effective use of posterior thoracolumbosacral screws in patients as young as one year of age without evidence of adverse effects related to alteration of future vertebral growth of immature spinal segments. In addition, the accuracy of pedicle screw placement in the pediatric population exceeds the accuracy rate reported in the adult patient population.

As it is important that device sponsors have a clear regulatory pathway for spinal devices indicated for the pediatric population, modification of the indications for use under 21 CFR 888.3070 is proposed to more accurately reflect the population currently regulated under 21 CFR 888.3070. FDA emphasizes that this reclassification is intended only to address the intended use of pedicle screw spinal systems used as an adjunct to fusion.

FDA's proposed indications for use is silent regarding patient age, as the language regarding use of posterior thoracolumbosacral screw fixation in skeletally mature subjects has been removed, which implies that use would be warranted in both the skeletally mature and immature population. FDA recognizes that it is current standard of care to use pedicle screw fixation techniques when a patient's osseous structure is dimensionally adequate to accommodate screw placement. As such, this may include subjects that are currently classified by FDA's CDRH as pediatric ($\leq$ 21 years) patients (See Table 1). While the FDA considers pediatric medical devices as those devices intended to treat or diagnose diseases or conditions from birth through age 21, it is important to note that the FDA does not only consider the patient's age when including this special patient population, but more so the presence of adequate bone structure to accommodate screws in the posterior thoracolumbosacral spine.

Table 1. FDA/CDRH Definitions of Pediatric Population Subgroups

Description	Age
Neonate / Newborn	From birth to 1 month of age
Infant	Greater than 1 month to 2 years of age
Child	Greater than 2 to 12 years of age
Adolescent	Greater than 12 to 21 years of age

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089740.htm

The purpose of this reclassification panel meeting is to gather information from the panel regarding the safety and effectiveness of pedicle screw use for the Class III indications described in 21 CFR 888.3070(b)(2). This includes pedicle screw treatment for DDD and spondylolisthesis other than either severe spondylolisthesis (grades 3 and 4) at L5-S1 or degenerative spondylolisthesis with objective evidence of neurologic impairment. The information in this appendix is intended to demonstrate that the safety and effectiveness of pedicle screw use for Class II and III indications in skeletally immature patients is not different than the safety and effectiveness of pedicle screw use in skeletally mature patients for the Class II indications outlined in 21 CFR 888.3070(b)(1). As outlined by the regulatory history above, Class II indications such as scoliosis, trauma, and fracture/dislocation, as well as Class III indications such as spondylolisthesis, have already been cleared for use in the pediatric population. Thus, in order to ensure consistency and properly classify all indications to Class II, it is necessary to eliminate the 'skeletally mature' designation from 21 CFR 888.3070(b)(1) when redefining the indications for pedicle screw spinal systems.

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13. Appendix B: Supporting Information for Dynamic Stabilization Systems and 522 Orders

Current Status:

Table 1: Section 522 Postmarket Surveillance Orders Issued 10/5/2009 (as of 3/23/2013)

PS090002	Alphatec Spine	Zodiac Dynamo Semi-rigid Spinal System	Other
PS090003	Applied Spine Technologies	Bar Pedicle Screw Spinal Fixation System	Other
PS090004	Biospine Co.	Bioflex	Other
PS090005	DePuy Spine	6.35mm and 5.5mm PEEK rods	Terminated
PS090006	Globus Medical,	Protex rods	Other
PS090007	Globus Medical	Transition Stabilization System	Study Pending
PS090008	Medtronic Sofamor Danek	CD Horizon PEEK rods	Study Pending
PS090009	Medtronic Sofamor Danek	CD Horizon Agile Dynamic Stabilization Device	Other
PS090010	Synthes Spine	Ngarde System	Other
PS090011	Paradigm Spine	DSS Stabilization System	Progress Inadequate
PS090012	Alphatec Spine	Isobar Semi-rigid Spinal System & Dual Dampener	Other
PS090013	Ulrich Medical USA	SSCS Hinged Screws	Other
PS090014	Ulrich Medical USA	Cosmic System	Other
PS090015	Exactech.	Modified Vertiflex Spinal Screw System (with Dynabolt rods)	Study Pending
PS090016	Zimmer Spine	Zimmer® Dynesys® Spinal System with DTO implant	Progress Inadequate

PS090017	Zimmer Spine	Zimmer® Dynesys® Top-loading Spinal System	Progress Inadequate

*http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pss.cfm

Current Status Definitions

Status	Definition
Study Pending	The plan has been approved, but no subjects have been enrolled.
Progress Inadequate	The study has begun, but the study progress is inconsistent with the plan (e.g., not meeting enrollment schedule, missing timepoint evaluations, poor follow-up rates, not all endpoints evaluated).
Terminated	The sponsor has not fulfilled or cannot fulfill the postmarket surveillance order (e.g., study questions are no longer relevant, sponsor withdraws premarket application, dataset cannot address 522 order), and, after all appropriate efforts to fulfill the order have been exhausted, FDA has terminated the study. This is a final study status.
Other	The study status does not fit another category (e.g., change in ownership underway, redesigning device and need prior premarket clearance/approval to use in study, device has been cleared or approved but is not currently marketed). This is an interim study status.

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm268064.htm

Literature Review

In an effort to comprehensively understand the adverse events associated with DSSs, the Orthopedic Spinal Devices Branch (OSDB) conducted a literature review. The original literature search was conducted in 2008 and 2009 in support of the 522 Orders. This search was updated in March 2013 and is provided here for consideration by the panel.

Literature Search Methods:

A search was conducted of adverse events with posterior, pedicle screw-based stabilization systems for fusion and non-fusion uses in the lumbar spine. The search was conducted using three databases (PubMed, Web of Science, and Embase) through 12/31/2013. The search terms used were:

Pubmed

Publication date from 2009/01/01 to 2013/12/31, English
(adverse OR complication OR risk OR safety OR injury OR malfunction* OR equipment failure OR undesirable OR tolerability OR mortality OR morbidity OR contraindicat*[Text Word])
OR
(adverse OR complicat*)
AND
(stabilization OR stabilisation) AND pedicle AND lumbar

AND
(dynesys OR graf OR dynabolt OR isobar OR dss OR bioflex OR axient OR agile OR ponte OR PEEK OR NFIX OR NHANCE OR NFLEX OR TOPS OR FASS)
OR
("x-rod" OR "x rod" OR "fulcrum-assisted" OR "fulcrum assisted"[Text Word])

Web of Science

Databases=SCI-EXPANDED Timespan=2009-01-01 - 2013-02-06
TS=(pedicle) AND TS=(lumbar)
AND
Topic=("x rod" OR "nfix II" OR "modular tops") OR Topic=(PEEK OR agile OR ponte OR stabilimax OR fass OR dto OR nflex OR nhance) OR Topic=(dynesys OR graf OR dynabolt OR isobar OR bioflex OR axient OR accuflex)
AND
TS=(complication*) OR TS=(adverse) OR TS=(injur*) OR TS=(malfunction*) OR TS=(safe*) or TS=("equipment failure") or TS=(contaminat*) OR TS=(risk*)

Embase

[english]/lim AND [2009-2013]/py
adverse OR complicat* OR 'risk'/exp OR risk OR 'safety'/exp OR safety OR 'injury'/exp OR injury OR malfunction* OR 'equipment'/exp OR equipment AND failure OR 'equipment failure'/exp OR undesirable OR tolerability OR 'mortality'/exp OR mortality OR 'morbidity'/exp OR morbidity OR contraindicat*)
AND
(lumbar OR 'lumbar spine'/exp
AND
'pedicle screw'/exp OR 'spine pedicle fixation device'/exp OR pedicle
AND
stabilization OR stabilisation OR 'spine fixation device'/exp OR 'spine stabilization'/exp)
AND
dynesys OR graf OR dynabolt OR isobar OR 'dss'/exp OR dss OR bioflex OR axient OR agile OR ponte OR peek OR nfix OR nhance OR nflex OR tops OR fass OR 'x-rod' OR 'x rod' OR 'fulcrum-assisted' OR 'fulcrum assisted'

Results:

The initial search through September of 2009 yielded 40 literature articles on various topics. An additional 28 articles were identified in the time period of 1/1/2009 – 12/31/2013. In addition, 13 unique articles were identified via indication-specific concurrent searches for spondylolisthesis and DDD in the 1/1/2009 – 12/31/2013 time frame. Eight articles were excluded for either describing an unrelated device, or not being written in English. Four articles were unavailable at the time of this review.

Table 2: Devices Discussed in Literature

Device	**Frequency: up to 2009 (initiation of 522 Orders)**	**Frequency: 2009-present**
Dynesys	22	13
Dynesys DTO	0	4
Graf	12	14
AccuFlex	2	1
DSS	2	0
FASS	2	0
Leeds-Keio	2	0
PEEK Rods	2	5

PEEK-CF Rods	0	1
Twinflex (Eurosurgical)	2	1
BioFlex	1	2
Claris (Eurosurgical)	1	0
IsoBar	1	0
N Fix II/NFlex	1	2
Stabilimax NZ	1	1
TOPS	0	2

Table 3: Number of Articles that Discussed Fusion vs. Non-Fusion Intended Use

Intended Use	**Frequency: up to 2009 (initiation of 522 Orders)**	**Frequency: 2009-present**
Fusion	11	5
Non-Fusion	36	15
Hybrid	0	7

It is evident from the literature that the predominant devices being discussed in the clinical community are the Dynesys and Graf devices, though there is growing interest in PEEK rods, especially for fusion. In addition, the predominant intended use being studied is non-fusion. There is growing interest in hybrid use, which may be due to the FDA clearance and subsequent availability of the Dynesys DTO transition implant, which was designed to allow Dynesys and a rigid system to be implanted at adjacent levels for stabilization as an adjunct to fusion.

Discussion of Adverse Events in Reports of Fusion Use, by System, in the 2009-present Studies:

There have been no new reports of fusion use for Dynesys.

In a report of a system used primarily in Europe (Graf Ligamentoplasty), Kanayama (2009) described adjacent segment disease in 9.2% (6/65 patients) in the Graf ligamentoplasty group for fusion. One of these patients required additional surgery.

There are increasing amounts of data available on fusion use of PEEK rods. Ormond (2012) reported on a retrospective case series of PEEK rods used for fusion. Eight (8) out of 42 (20%) patients underwent a further surgery secondary to the progression of lumbar spine degenerative disease or instrumentation failure. The most common reason for revision was adjacent level disease: 5 out of 8 re-operations (62.5%). DeIure (2012) reported on 30 patients with degenerative spine disease retrospectively and found two early complications: one superficial wound dehiscence and one deep infection. One patient showed cranial screw mobilization at 8 months follow up. All patients with PEEK rods and interbody devices fused by 12 months. Three (3) patients with posterior fusion only had incomplete fusions at 8, 16, and 18 months (last visit).

Literature Conclusions:

There appears to be a trend towards focus on fusion/hybrid uses though the utility of these devices for fusion is questioned (Schroeder, 2012). While adverse events in non-fusion devices were not inconsistent with rigid fusion (Coe, 2012), and adjacent segment morbidity appeared to be lower than in rigid fusion surgeries (Kanayama, 2009), additional studies with more long term follow up is necessary (Kelly, 2010).

Initial results for PEEK rods suggest that a less constrained device may result in lower fusion rate and higher fracture rate. Despite relatively short follow up, there is no evidence that PEEK rods are superior to titanium rods in resulting fusion, and there may actually be an increased risk of reoperation in comparison to fusion using titanium rods (Ormond, 2012). Mis-matching biomechanics between the rod curvature and the patient's natural lordosis may have an effect on screw loosening and other short-term complications (DeIure, 2012).

While not the focus of this search, significant effort is underway to further study these devices biomechanically; these studies attempt to qualify and quantify: 1) the motion characteristics of the instrumented and adjacent segments; 2) potential effect on surrounding tissue; and 3) the optimal biomechanics for the intended use. In a retrieval analysis, retrieved polycarbonate urethane spacers of the Dynesys system exhibited evidence of *in vivo* damage and chemical degeneration, correlated with implantation time (Ianuzzi 2010). Additional PEEK materials are being considered for fusion use, taking into account the biomechanical properties of alternative materials (Bruner 2010). In non-clinical cadaver work, it is suggested that the non-linearity of the spine needs to be taken into account when designing these implants (Kim 2011).

Given the lack of data available on these systems (literature, prospective studies, etc), FDA believes that the safety and effectiveness profile for DSSs are not well established, the risks to health are not fully characterized for this device subtype, and special controls cannot be developed at this time to mitigate the risks to health.

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14. Appendix C: MAUDE Search Strategy and Results

MAUDE Search Strategy

Multiple queries were created to identify all relevant MDRs from the MAUDE Database. The searches used the following parameters: date entered and product code. The date range was restricted to January 1, 2003 through December 31, 2012. The results were exported from MAUDE and unduplicated for review. Only unique reports were counted towards the final results.

A summary of all search criteria and results are displayed in the table below.

Table 1: Search criteria

	Search 1	Search 2	Search 3	Search 4	Search 5	Search 6
Date entered	January 1, 2003 – December 31, 2012					
Product code	NKB	MNH	MNI	NQP	OSH	KWP
MDR Results	2893	725	914	500	1	3893
Relevant MDRs[1]	1733	375	763	463	1	3260

[1]Relevant MDRs are the reports that remained after removal of duplicate reports.

Reports were utilized exactly how they were found in MAUDE. No fields (e.g., product code, device problem code) were corrected or changed, thereby providing a more accurate representation of the information in MAUDE.

Reports were defined as duplicates and removed from analysis when all of the following fields were identical: date received, date of event, date implanted, date implant removed, patient age, patient gender, and reporter city.

Results

A total of 6,595 unique MDRs were found related to the product codes associated with pedicle screw spinal systems from 2003 through 2012. The reports were separated by product codes for comparison based on how they are used:

- NKB represents the Class III indication of DDD and other types of spondylolisthesis other than severe spondylolisthesis (grades 3 or 4) or degenerative spondylolisthesis with objective evidence of neurologic impairment;
- MNH and MNI are used for pedicle screw fixation Class II uses;
- NQP is used for dynamic stabilization systems (DSS);
- OSH is a newer product code for adolescent idiopathic scoliosis (AIS); and
- KWP is used for posterior, non-pedicle based components (e.g., hooks, spinous process plates), but these components are often included as part of pedicle screw spinal systems.

The MDRs were reported under the event types shown in Table 2.

Table 2: Event Types

Product code	Event type				
	Injury	Malfunction	Death	Other	Invalid data or blank
NKB	898	786	1	34	14
MNI & MNH	638	455	2	35	7
NQP	317	133	--	10	2
OSH	--	1	--	--	--
KWP	1902	1243	19	54	28

Figure 1 displays the date the MDR was received by FDA.

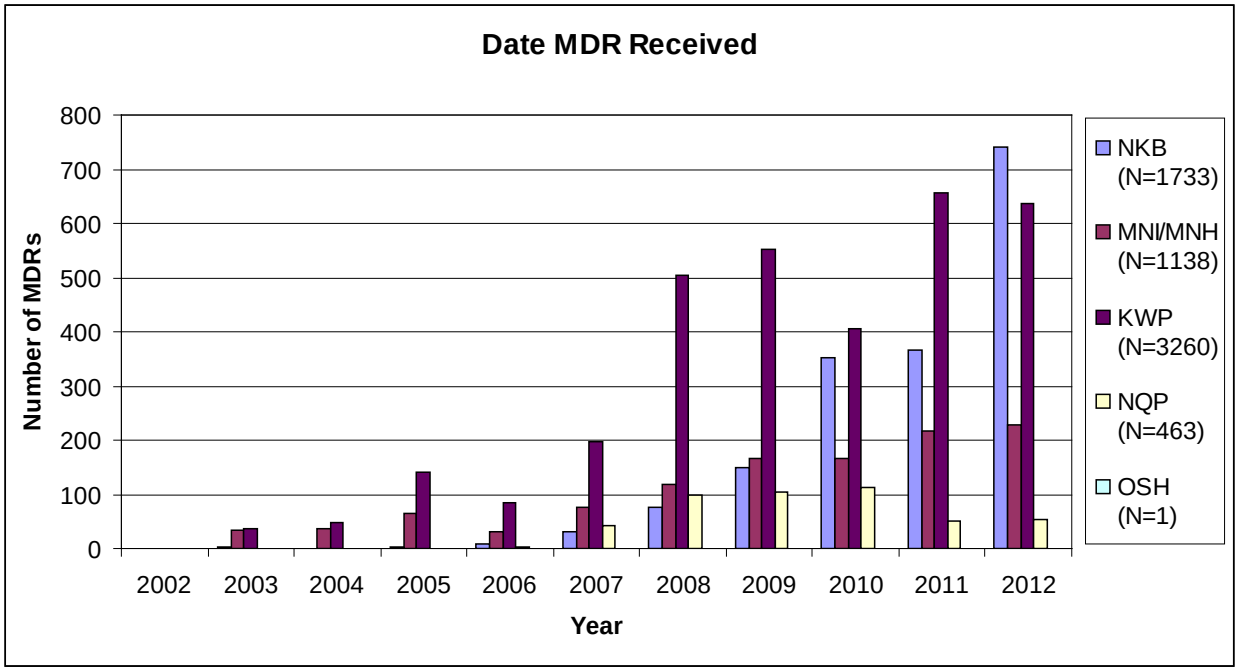

Figure 1. MDR date received (Note: While not visible in the figure, one MDR for KWP was received in 2002, and the one OSH MDR was received in 2011.)

Of the 6,595 reports, 2,744 contained both the date of implantation and the date of event, allowing the time to adverse event occurrence to be calculated. These can be seen in Figure 2. Note the counts represent the time to event that occurred within the year shown on the x-axis. For example, 56 events occurred within the second year of implantation for product code NKB (i.e., between one and two years after implantation).

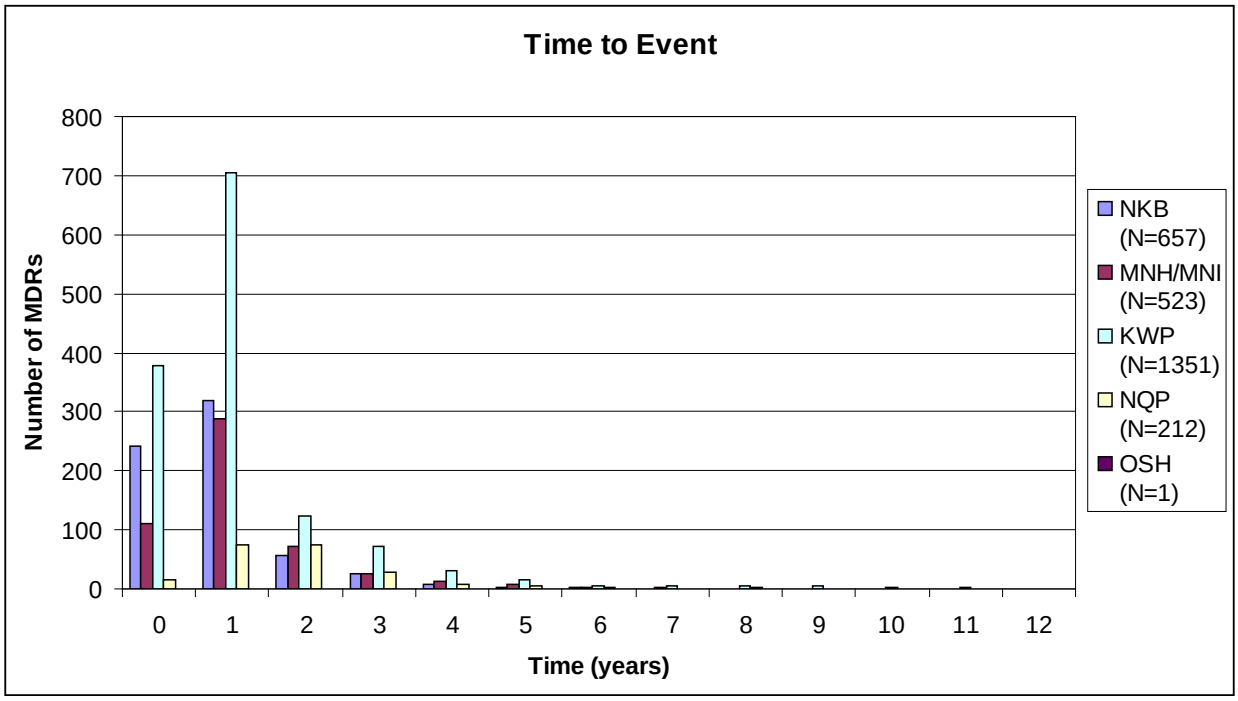

Figure 2. Time from implantation to event occurrence